07 December 2022
EMA/926734/2022
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment report

Olumiant

International non-proprietary name: baricitinib

Procedure No. EMEA/H/C/004085/II/0028

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	29 Apr 2021	29 Apr 2021	☐
☐	CHMP Rapporteur Assessment Report	22 Jun 2021	22 Jun 2021	☐
☐	PRAC Rapporteur Assessment Report	25 Jun 2021	25 Jun 2021	☐
☐	PRAC members comments	30 Jun 2021	30 Jun 2021	☐
☐	Updated PRAC Rapporteur Assessment Report	01 Jul 2021	01 Jul 2021	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	08 Jul 2021	08 Jul 2021	☐
☐	CHMP members comments	12 Jul 2021	12 Jul 2021	☐
☐	Updated CHMP Rapporteur Assessment Report	15 Jul 2021	16 Jul 2021	☐
☐	Request for supplementary information	22 Jul 2021	22 Jul 2021	☐
☐	Submission of MAH responses	13 Aug 2021	13 Aug 2021	☐
☐	Re-start of procedure	16 Aug 2021	16 Aug 2021	☐
☐	CHMP Rapporteur Assessment Report	14 Sep 2021	17 Sep 2021	☐
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☐	CHMP members comments	04 Oct 2021	04 Oct 2021	☐
☐	Updated CHMP Rapporteur Assessment Report	07 Oct 2021	08 Oct 2021	☐
☐	Request for supplementary information	14 Oct 2021	14 Oct 2021	☐
☐	MAH request for timetable extension	n/a	07 Mar 2022	☐
☐	Submission of MAH responses	20 May 2022	13 May 2022	☐
☐	Re-start of procedure	23 May 2022	23 May 2022	☐
☐	CHMP Rapporteur Assessment Report	21 June 2022	21 June 2022	☐
☐	PRAC Rapporteur Assessment Report	24 June 2022	24 June 2022	☐
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☐	Updated PRAC Rapporteur Assessment Report	30 June 2022	n/a	☐
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Status of this report and steps taken for the assessment				
☐	Updated CHMP Rapporteur Assessment Report	14 July 2022	20 July 2022	☐
☐	Request for supplementary information	21 July 2022	21 July 2022	☐
☐	Submission of MAH responses	14 Oct 2022	10 Oct 2022	☐
☐	Re-start of procedure	17 Oct 2022	17 Oct 2022	☐
☐	CHMP Rapporteur Assessment Report	15 Nov 2022	16 Nov 2022	☐
☐	PRAC Rapporteur Assessment Report	18 Nov 2022	17 Nov 2022	☐
☐	PRAC members comments	23 Nov 2022	23 Nov 2022	☐
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☐	CHMP members comments	05 Dec 2022	05 Dec 2022	☐
☐	Updated CHMP Rapporteur Assessment Report	08 Dec 2022		☐
☐	Request for supplementary information/Opinion	15 Dec 2022		☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

Criteria for PRAC plenary discussion: proposal for update of SmPC/PL, introduction of or changes to imposed conditions or additional risk minimisation measures (except for generics aligning with the originator medicinal product), substantial changes to the pharmacovigilance plan (relating to additional pharmacovigilance activities, except for generics adapting aligning with the originator medicinal product), substantial disagreement between the Rapporteur and other PRAC members, at the request of the Rapporteur, any other PRAC member, the Chair or EMA.

[3] Sections related to Risk Management Plan or on non-interventional PASS results. If PRAC advice was ad hoc requested by the CHMP, the relevant Attachment to the assessment report applies and has been endorsed by the PRAC.

Procedure resources	
CHMP Rapporteur: CHMP Co-Rapporteur	Johann Lodewijk Hillege (NL) Christophe Focke (BE)

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List of abbreviations

Acronym or Term	Definition
ACTT	Adaptive COVID Treatment Trial
AD	atopic dermatitis
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BSV	between-subject variability
CHMP	Committee for Medicinal Products for Human Use
CL/F	apparent total clearance of the drug from plasma after oral administration
Cmax	maximum (or peak) serum concentration
CPK	creatinine phosphokinase
CV	coefficient of variation
COVID-19	coronavirus disease 2019
DLQI	Dermatology Life Quality Index
DVT	deep vein thrombosis
EMA	European Medicines Agency
EU	European Union
HADS	Hospital Anxiety Depression Scale
HDL	high-density lipoprotein
HOME	Harmonizing Outcomes Measures in Eczema
IL	interleukin
IR	incidence rate
ITT	intent-to-treat
JAHV	Study paediatric patients with juvenile idiopathic arthritis
JAIP	Study paediatric patients with atopic dermatitis
JAGA	Study paediatric patients with type 1 interferonopathies
JAK	Janus kinase
LDL	low-density lipoprotein
KHAA study	PK study in adult COVID-19 patients on mechanical ventilation

MACE	major adverse cardiovascular events
MCID	minimal clinically important difference
NMSC	non-melanoma skin cancer
NRS	numeric rating scale
PBI	Patient Benefit Index
PE	pulmonary embolism
PK	pharmacokinetics
PRO	patient-reported outcomes
PROMIS	Patient-Reported Outcomes Measurement Information System
pSTAT	phosphorylated signal transducer and activator of transcription
pSTAT3	phosphorylated signal transducer and activator of transcription 3
QoL	quality of life
RA	rheumatoid arthritis
RMP	risk management plan
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory coronavirus 2
SCE	Summary of Clinical Efficacy Module 2.7.3
SCS	Summary of Clinical Safety Module 2.7.4
SmPC	Summary of Product Characteristics
SOC	system organ class
STAT	signal transducer and activator of transcription
t1/2	elimination half life
TCI	topical calcineurin inhibitors
TCS	topical corticosteroids
TE	treatment-emergent
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
URTI	upper respiratory tract infection
V/F	apparent volume of distribution
VTE	venous thromboembolism
WHO	World Health Organisation

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Eli Lilly Nederland B.V. submitted to the European Medicines Agency on 27 April 2021 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

C.I.6 - Extension of indication to include treatment of coronavirus disease 2019 (COVID 19) in hospitalised adult and paediatric patients aged 10 years and older who require low-flow oxygen or non-invasive ventilation/high flow oxygen for Olumiant; as a consequence, sections 4.1, 4.2, 4.4, 4.6, 4.8, 5.1, 5.2, 6.6 of the SmPC are updated. The Annex II and the Package Leaflet are updated in accordance. Version 11.1 of the RMP has also been submitted.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0062/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0062/2021 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Not applicable

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

See separate CHMP assessment report of the MAH's request.

Scientific advice

The MAH did not seek Scientific advice at the CHMP.

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

End of December 2019, the World Health Organization (WHO) was informed about a cluster of cases of viral pneumonia of unknown cause in Wuhan, China. In mid-January 2020, the pathogen causing this atypical pneumonia was identified as a novel coronavirus, severe acute respiratory coronavirus 2 (SARS-CoV-2) and genome sequence data were published. Since then, the virus has spread globally, and on 30 January 2020, the WHO declared the outbreak a Public Health Emergency of International Concern and on 11 March 2020 a pandemic. The pandemic is ongoing despite unprecedented efforts to control the outbreak.

SARS-CoV-2 is a highly transmissible and pathogenic coronavirus that causes COVID-19. The majority of SARS-CoV-2-infected patients experience mild respiratory disease, generally affecting the lower respiratory tract. However, following infection, some patients develop a cytokine storm that manifests clinically as a hyperinflammatory state (persistent fever, elevated inflammatory markers, and multiple organ dysfunction) with pulmonary involvement. Severe cases can progress with complications such as multi-organ failure, cardiac complications (arrhythmias, shock), pulmonary failure, ARDS, thromboembolic complications, neurologic complications such as encephalopathy, inflammatory complications, including anaemia, thrombocytopenia and result in death.

The MAH claimed the following therapeutic indication:

"Olumiant is indicated for the treatment of coronavirus disease 2019 (COVID 19) in hospitalised adult and paediatric patients aged 10 years and older who require low-flow oxygen or non-invasive ventilation/high flow oxygen (see section 5.1)."

Epidemiology and risk factors

According to the WHO, as of 12 June 2021, 174 million cumulative cases and 3.78 million deaths globally have occurred since the start of the pandemic (https://covid19.who.int/). The majority of infections result in asymptomatic or mild disease with full recovery.

Underlying health conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease, chronic kidney disease, immune-compromised status, cancer and obesity are considered risk factors for developing severe COVID-19. Other risk factors include organ transplantation and chromosomal abnormalities.

Increasing age is another risk factor for severe disease and death due to COVID-19. European countries that have established surveillance systems in long-term care facilities (LTCF) have reported that 5-6% of all current LTCF residents died of COVID-19, and that LTCF residents accounted for up to 72% of all COVID-19 related deaths.

Individuals with high risk of exposure to SARS-CoV-2 due to occupation include healthcare and frontline workers.

Aetiology and pathogenesis

SARS-CoV-2 is a positive-sense single-stranded RNA (+ssRNA) virus with a single linear RNA segment. It is enveloped, and the virions are 50–200 nanometres in diameter. Like other coronaviruses, SARS-CoV-2 has four structural proteins, known as the S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins.

The spike protein contains a polybasic cleavage site, a characteristic known to increase pathogenicity and transmissibility in other viruses. The Spike is responsible for allowing the virus to attach to and fuse with the membrane of a host cell. The S1 subunit catalyses attachment to the angiotensin-converting enzyme 2 (ACE-2) receptor present on cells of the respiratory tract, while the S2 subunit facilitates fusion with the cell membrane. The spike protein is the main target antigen for vaccine development and treatment options such as monoclonal antibodies, because it was shown that antibodies directed against it neutralise the virus and it elicits an immune response that prevents infection in animals.

The virus belongs to the beta-coronaviruses. It is believed that SARS-CoV-2 has zoonotic origins and it has close genetic similarity to bat coronaviruses.

Human-to-human transmission of SARS-CoV-2 was confirmed in January 2020. Transmission occurs primarily via respiratory droplets from coughs and sneezes and through aerosols. The median incubation period after infection to the development of symptoms is four to five days. Most symptomatic individuals experience symptoms within two to seven days after exposure, and almost all symptomatic individuals will experience one or more symptoms before day twelve. Common symptoms include fever, cough, fatigue, breathing difficulties, and loss of smell and taste, and symptoms may change over time.

The major complication of severe COVID-19 is acute respiratory distress syndrome (ARDS), presenting with dyspnoea and acute respiratory failure that requires mechanical ventilation. In addition to respiratory sequelae, severe COVID-19 has been linked to cardiovascular sequelae, such as myocardial injury, arrhythmias, cardiomyopathy and heart failure, acute kidney injury often requiring renal replacement therapy, neurological complications such as encephalopathy, and acute ischemic stroke.

Clinical presentation, diagnosis

The severity of COVID-19 varies. The disease may take a mild course with few or no symptoms, resembling other common upper respiratory diseases such as the common cold. Mild cases typically recover within two weeks, while those with severe or critical diseases may take three to six weeks to recover. Among those who have died, the time from symptom onset to death has ranged from two to eight weeks. Prolonged prothrombin time and elevated C-reactive protein levels on admission to the hospital are associated with severe course of COVID-19 and with a transfer to ICU.

The gold standard method of testing for the presence of SARS-CoV-2 is the reverse transcription-polymerase chain reaction (RT-PCR), which detects the presence of viral RNA fragments. As this test detects RNA but not an infectious virus, its ability to determine the duration of infectivity of patients is limited. The test is typically done on respiratory samples obtained by a nasopharyngeal swab, a nasal swab or a sputum sample.

Management

The management of COVID-19 cases has developed during 2020, and includes supportive care, which may include fluid therapy, oxygen support, and supporting other affected vital organs.

The major classes of therapies developed to treat COVID-19 infection in hospitalised patients are

- antiviral therapies, thought to be most efficacious earlier in the course of the disease, by limiting replication of SARS-CoV-2,
- immunosuppressive/anti-inflammatory therapies, considered most useful in the hyperinflammatory phase of the condition, where the inflammatory response to viral infection leads to tissue damage, and
- monoclonal antibodies.

Veklury (remdesivir), an antiviral therapy, is approved in Europe for the treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment (VEKLURY SmPC 2021).

In addition, dexamethasone, an anti-inflammatory therapy, is approved in Europe for the treatment of COVID-19 in adult and adolescent patients aged 12 years and older with body weight at least 40 kg who require supplemental oxygen therapy (Dexamethasone SmPC).

Anakinra, an IL-1 inhibitor, is approved for use in the EU for the treatment of COVID-19 in adults with pneumonia requiring supplemental oxygen who are at risk of progressing to severe respiratory failure as defined by plasma suPAR level of ≥6 ng/mL.

The immunosuppressive/anti-inflammatory therapy tocilizumab is approved in Europe for the treatment of COVID-19 in adults receiving systemic corticosteroids and requiring supplemental oxygen or mechanical ventilation.

In addition several monoclonal antibodies have been approved for treatment of confirmed COVID-19 in patients who do not require supplemental oxygen and who are at high risk of their COVID-19 disease becoming severe or for prevention of COVID-19 (including Ronapreve, Regkirona, Xevudy and Evusheld).

WHO in their living guideline on therapeutics and Covid 19 recommended for patients with severe or critical COVID-19 (v10.0 published 22/04/2022) issued (amongst other recommendations):

- a strong recommendation for systemic corticosteroids;
- a strong recommendation for interleukin-6 (IL-6) receptor blockers (tocilizumab or sarilumab), in combination with corticosteroids;
- a strong recommendation for baricitinib as an alternative to IL-6 receptor blockers, in combination with corticosteroids;

In Europe and other countries, while a number of vaccines have recently received approval or are currently in development (preventive treatment targeting the general public), an important unmet need remains for patients hospitalised with more severe disease.

2.1.2. About the product

Baricitinib is a selective and reversible inhibitor of Janus kinase (JAK)1 and JAK2. Baricitinib has been approved for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs,

for the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy and for the treatment of severe alopecia areata in adult patients.

Baricitinib was identified as a potential intervention for the treatment of COVID-19 based on baricitinib's known anti-cytokine properties and the hypothesis of a host antiviral mechanism. Baricitinib reduces levels of cytokines and biomarkers implicated in COVID-19, including IL-6, IFN-γ, MCP-3, CXCL10, IL-10, MCP-2, CCL19, PTX3, and IL-27. In addition, markers that are decreased in moderate to severe COVID-19 patients were increased in response to baricitinib and include CCL17, GDF2, and SCF (Sims et al. 2021).

Baricitinib has been identified as a numb associated kinase (NAK) inhibitor with a high affinity for AP2 associated protein kinase 1 (AAK1), BIKE and GAK. Specific NAK's AAK1 and GAK are linked to SARS-CoV-2 (COVID-19) entry in human cells.

EMA's safety committee, PRAC, has started a review of the safety of Janus kinase (JAK) inhibitors used to treat several chronic inflammatory disorders (rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, ulcerative colitis and atopic dermatitis).

The review was prompted by the final results from a clinical trial (study A3921133) of the JAK inhibitor Xeljanz (tofacitinib). The results showed that patients taking Xeljanz for rheumatoid arthritis and who were at risk of heart disease were more likely to experience a major cardiovascular problem (such as heart attack, stroke or death due to cardiovascular disease) and had a higher risk of developing cancer than those treated with medicines belonging to the class of TNF-alpha inhibitors. The study also showed that compared with TNF-alpha inhibitors, Xeljanz was associated with a higher risk of death due to any cause, serious infections, and blood clots in the lungs and in deep veins (venous thromboembolism, VTE).

In addition, preliminary findings from an observational study involving Olumiant (baricitinib), also suggest an increased risk of major cardiovascular problems and VTE in patients with rheumatoid arthritis treated with Olumiant compared with those treated with TNF-alpha inhibitors.

In the treatment of inflammatory disorders, Olumiant and other JAK inhibitors work in a similar way to Xeljanz. PRAC will therefore carry out a review to determine whether these risks are associated with all JAK inhibitors authorised in the EU for the treatment of inflammatory disorders and whether the marketing authorisations for these medicines should be amended.

The review of JAK inhibitors in the treatment of inflammatory disorders has been initiated at the request of the European Commission (EC) under Article 20 of Regulation (EC) No 726/2004 and is currently on-going.

However, the PRAC decided to exclude the COVID-19 indication from the referral: janus-kinase-inhibitors-jaki-article-20-referral-addendum-notification_en.pdf (europa.eu).

2.1.3. The development programme/compliance with CHMP guidance / scientific advice

No EMA or FDA scientific guideline was available for the development of treatments for COVID-19 at the start of Study ACTT-2 and Study KHAA. In May 2020, the FDA published Guidance for Industry entitled, COVID-19: Developing Drugs and Biological Products for Treatment or Prevention (FDA 2020).

While no formal European Scientific Advice was sought regarding the COVID-19 application, consultations were held between the MAH and EMA, FDA, Pharmaceuticals and Medical Devices Agency, and other regulatory agencies to align on the strategy for submission and content of the common technical document dossier.

Based upon the CSR of the ACTT-2 and the topline results of the KHAA, CHMP granted review under accelerated assessment, provided that the full CSR of the KHAA would be submitted with the application.

2.1.4. General comments on compliance with GCP

See 5.4.1.

2.2. Quality aspects

New quality data are presented to support the alternate administration of baricitinib 2 mg and 4 mg tablets for COVID-19 treatment. The alternate administration of the baricitinib tablets focuses on tablets dispersed in water followed by oral administration (swallowing), or, enteral administration, specifically using gastrostomy or nasogastric/orogastric tubing for delivery to the stomach.

The alternate administration of tablets has been investigated by the MAH in view of the multiple indications for baricitinib applied globally with different patient populations. This results in different potential dosing regimens with different approved tablet strengths available globally. Consequently, the analytical studies in the newly submitted pharmaceutical development section 3.2.P.2.2 also refer to an additional tablet 1 mg strength (lowest dose currently applied globally) and a dosing range (1 mg to 6 mg) which covers all potential indications.

CHMP's comments:

The alternative administration (oral dispersion, gastrostomy tube, nasogastric/orogastric tube) is restricted to COVID-19 treatment.

The present variation application does not intend to add a new 1 mg dosage strength in view of the current indication and newly proposed indication for treatment of COVID 19. However, it is included in the documentation because it is part of the overall bracketing approach used to support the range of doses, administration routes, and gastrostomy and nasogastric/orogastric enteral tube sizes and material of construction that may be used for all potential indications.

Tablet formulation overview

The development of baricitinib 2 mg and 4 mg tablets has been provided in the initial marketing authorisation submission for the rheumatoid arthritis indication.

A 1 mg tablet strength was developed afterwards and used in clinical trials for other indications. Baricitinib drug substance has been demonstrated to be stable. Stress stability data was generated in solution over a pH range of 1 - 13 at 70° C. Due to the low aqueous solubility of baricitinib, acetonitrile was used as a co-solvent. No degradation of baricitinib was observed below pH 7. Even at these high temperatures, only minor degradation was seen from pH 7 to pH 8. The photostability of baricitinib in both buffered and unbuffered (water/ACN) solutions was assessed by exposure to high-intensity fluorescent light. No significant degradation was observed in any of the solutions exposed to intense fluorescent light.

CHMP's comments:

No additional warnings or labelling statements are necessary as per the Guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'.

Alternate administration overview

The 1 mg tablet strength is the lowest tablet strength manufactured globally and represents the lowest current dose, whereas the highest potential single dose for any future indication was identified as 6 mg, which could be achieved with a combination of 1 mg, 2 mg and/or 4 mg tablets. The 1 mg and 2 mg tablets were used in the analytical studies to bracket 1 mg to 6 mg dose levels. The 2-mg tablet has the worst-case excipient load along with higher potential drug loss compared to the 4-mg tablet for the same core tablet weight.

Table P.2.2.2-1 Analytical Study Relationship to Represented Dose

Analytical Study	Total Core Tablet Weight	Dose Represented Based on Total Solids Load	Tablets to Achieve Dose
1 x 1-mg tablet	100 mg	1 mg	1 x 1-mg tablet
1 x 2-mg tablet	200 mg	2 mg	2 x 1-mg tablet
			1 x 2-mg tablet
		4 mg	1 x 4-mg tablet
2 x 2-mg tablet	400 mg	4 mg	2 x 2-mg tablet
		6 mg	1 x 2-mg tablet and 1 x 4-mg tablet
3 x 2-mg tablet	600 mg	6 mg	3 x 2-mg tablet

A bracketing study with small (12 Fr) and large (20 - 24 Fr) diameter silicone and polyurethane gastrostomy tubes (G-tube) was evaluated first. Later, an additional study to assess inclusion of nasogastric/orogastric tubes (NG/OG-tube) with smaller diameter (8 Fr) into the bracket, as well as assessing tubing with PVC material of construction was performed.

Oral dispersion in water

Crushed tablet dispersion stability

The stability of crushed tablets in water was examined with 2 mg tablets which are representative for the stability of the 1 mg and 4 mg tablets. Two single 2 mg tablets were crushed and aqueous dispersions were stored at ambient conditions up to 48 hours. A small degradation was observed.

Whole tablet dispersion for oral administration

Delivered dose is evaluated with 1 mg tablet (1 mg dose) and 3 x 2 mg tablets (6 mg dose) dispersed in 10 ml water and 10 mL to rinse the container. For the robustness study the same experiments were done with reduced amount of water for dispersing and rinsing (5 mL each). Stability of oral dispersion samples is evaluated in duplicate after 4 hours at ambient temperature for each tablet dose.

All results met the acceptance criteria (95 to 105% dose recovery) which supports one to three whole tablets being placed in 10 mL of water (5 mL minimum), gently swirling to disperse the tablets, administering within 4 hours, and then rinsing the container with 10 mL of water (5 mL minimum) to administer the full dose.

The product information indicates that it may take up to 5 to 10 minutes for the tablet to finely disperse which is acceptable for the oral administration.

Gastrostomy and Nasogastric/orogastric Tubes

Delivered dose, robustness, and compatibility experiments were performed on various doses dispersed in water and administered using various tube diameters and material types.

Tubing was evaluated by determining dose recovery with nominal dispersion and rinse volumes and also with decreased volumes to determine robustness of the administration. The physiochemical compatibility was determined by assessing dose recovery after remaining in the worst-case (largest surface area) tubing for at least 30 minutes.

The most common gastrostomy tube materials (silicone and polyurethane) were used for the G-tube studies. A bracketing approach was used regarding the tube diameter, 12 FR being the worst case for tube blockage, and 24 FR being worst case in terms of surface area. The most common NG/OG-tube materials are silicone, polyvinyl chloride (PVC), and polyurethane. Bracketing approach for tube diameter was also applied with detailed justification in the dossier whereas a maximal tube length was chosen to represent worst case in terms of surface area.

Based on standard availability of tube type and diameter, silicone and polyurethane were used for the delivered dose since the smaller diameter is worst-case for tube blockage, and PVC was used for the compatibility by holding the dispersion (or a portion of the dispersion due to tube volume) in the tube for up to 30 minutes. The volumes suggested for administration allow only a portion of the total volume to remain in the tube for the 30 minutes.

A summary of Gastrostomy and Nasogastric/Orogastric Tube Studies is provided in Table P.2.2.2.3-1

Table P.2.2.2.3-1 Summary of Gastrostomy and Nasogastric/Orogastric Tube Studies

Tablet	Silicone size, type (dispersion/rinse vol.)	Polyurethane size, type (dispersion/rinse vol.)	PVC size, type (dispersion/rinse vol.)
1 x 1-mg	8 Fr, NG/OG (20/10 mL or 25/5 mL) 12 Fr, G (15/15 mL or 10/10 mL) 24 Fr, G (15/15 mL or 10/10 mL)	8 Fr, NG/OG (20/10 mL or 25/5 mL) 12 Fr, G (15/15 mL or 10/10 mL) 20 Fr, G (15/15 mL or 10/10 mL)[a]	16 Fr, NG/OG (20/10 mL or 25/5 mL)
1 x 2-mg	8 Fr, NG/OG (25/14 mL)[b]	8 Fr, NG/OG (30/14 mL or 25/14 mL)	Not Studied
2 x 2-mg	8 Fr, NG/OG blockage[c]	8 Fr, NG/OG (30/15 mL)[d]	16 Fr, NG/OG (30/15 mL or 25/15 mL)
3 x 2-mg	12 Fr, G (15/15 mL or 10/10 mL) 24 Fr, G (15/15 mL or 10/10 mL)	10 Fr, NG/OG (30/15 mL or 25/15 mL) 12 Fr, G (15/15 mL or 10/10 mL) 20 Fr, G (15/15 mL or 10/10 mL)	Not Studied
Material of Construction Compatibility	Pass (24 Fr, G)	Pass (20 Fr, G)	Pass (16 Fr, NG/OG)

[a] Robustness study (10 mL dispersion/10 mL rinse) did not meet protocol criteria of 95% to 105% for 1 x 1-mg tablet in 20 Fr G-tube, however, were within 90% to 110% considered acceptable per EMA guidance.
[b] Robustness study (25 mL dispersion /14 mL rinse) passed. Delivered Dose study with nominal volumes (30 mL dispersion /14 mL rinse) had blockage of a replicate. Analyst inadvertently continued the analysis using a new tube to generate another replicate for n = 3 results. Although results met criteria, they did not pass due to tubing blockage.
[c] Blockage occurred with one replicate at each condition of nominal and reduced dispersion volume and study was not continued.
[d] Blockage occurred for one replicate in robustness study (25 mL dispersion/15 mL rinse) and study was not continued.

G-tubes studies

Delivered dose, compatibility, and robustness experiments were performed on 1 x 1-mg and 3 x 2-mg tablets (bracketing 1-mg and 6-mg doses) for G-tube administration. Robustness was assessed by

reducing the amount of water used for dispersion and rinsing. Compatibility was assessed by holding the dispersed dose in the G-tube for 30 minutes.

All delivered dose and compatibility experiments for G-tube dosing met pre-defined protocol acceptance criteria for the 1-mg and 6-mg doses. All robustness studies met protocol criteria (95% to 105% delivered dose) except for the 1-mg dose polyurethane 20 Fr G-tube. Still, the requirement of minimum 90% delivered dose was met as per EMA guidance.

The data support one to three whole tablets dispersed in 15 mL (10 mL minimum) of water, gently swirled until able to freely pass through the syringe tip and delivered through the tubing. To ensure the full dose is delivered, the container is rinsed with 15 mL (10 mL minimum) of water and delivered through the tubing.

NG/OG studies

All delivered dose and robustness experiments for NG/OG-tube dosing met acceptance criteria for the 1 x 1-mg tablet preparations for all tube types. The 2 x 2-mg tablets met acceptance criteria for delivered dose and robustness experiments with PVC tubing.

Passing results were achieved with 3 x 2-mg tablets using polyurethane 10 Fr tubing. The results of the delivered dose experiment for 2 x 2-mg tablets with polyurethane 8 Fr tubes passed the acceptance criteria. The robustness study had tube blockage in one replicate, therefore 30 mL dispersion is the minimum volume for 2 x 2-mg tablets. The results of the 1 x 2-mg tablets with polyurethane 8 Fr tubes passed the delivered dose and robustness studies.

Blockage occurred for delivered dose and robustness experiment replicates using the 2 x 2-mg tablets in silicone 8 Fr tubes and samples were not processed per protocol. The evaluation of 1 x 2-mg tablet preparation with the 8 Fr silicone tube also had blockage for one replicate with the nominal 30 mL dispersion volume. Although the results generated met criteria, due to tube blockage the test did not pass. The robustness study with 1 x 2-mg tablet with 8 Fr silicone tube passed without blockage of any tubes. A larger diameter silicone NG/OG tube was not available. However, the 12 Fr silicone G-tube experiment passed with 3 x 2-mg tablets with less water for dispersion (10 mL). Additionally, 10 Fr with polyurethane tubing passed with 3 x 2-mg tablets.

The data support one to three whole tablets dispersed in 30 mL of water, gently swirled until able to freely pass through the syringe tip and delivered through the polyurethane or PVC tubing. To ensure the full dose is delivered, the container is rinsed with 15 mL of water and delivered through the tubing. To avoid blockage of small diameter tubes, the syringe can be held horizontally and shaken during administration. The silicone tubing may have blockage issues at the 8 Fr size and if used, recommend only one tablet should be delivered with silicone 8 Fr tubing.

Overall conclusions of analytical studies

- Baricitinib tablets do not degrade in any meaningful amount when crushed and exposed to water for up to 48 hours.
- All delivered dose, robustness, and stability experiments for oral dispersion dosing met pre-defined protocol acceptance criteria for the 1-mg and 6-mg doses (at least 90% dose recovery as per EMA requirement)
- All materials of construction, silicone, polyurethane and PVC, are acceptable to use with baricitinib tablets. There are no issues with tube sizes 10 Fr and larger with up to three baricitinib tablets of any strength.

- Tubing with 8 Fr diameter may encounter blockage. Polyurethane tubing at 8 Fr was acceptable with delivering one tablet of 1 mg and 2 mg, and had three successful replicates delivering two tablets of 2 mg, but robustness (less water) was not completed due to blockage. Testing of silicone tubing at 8 Fr with two tablets of 2 mg was not completed due to blockage. One out of seven replicates using silicone 8 Fr tubing had blockage. Where samples were not blocked and processed, dose delivered data met criteria.

CHMP's comments:

In general, the MAH has considered the EMA Q&A on 'Administration of oral immediate release medicinal products through enteral feeding tubes' December 2018. A justification is given of the bracketing and worst-case approaches applied for the analytical studies and these are mostly acceptable.

The intrinsic stability of the drug substance baricitinib in solution (water and acetonitrile) was already demonstrated in the original registration with only minor degradation observed in the pH range 7 to 8. This is also reflected in the stability results of the dispersed tablets. The declared stability of 4 hours at room temperature is justified, yet the product information mentions to start the administration immediately after dispersion.

The studies for oral dispersion administration reveal no significant issues as the pre-set acceptance criteria are all met. For gastrostomy and nasogastric/orogastric administration a more complex bracketing design had to be set-up given the multiple factors to be studied. In summary, there are no compatibility issues between the plastic materials themselves and baricitinib under the conditions of the studies. In a number of cases, dose delivery and robustness results with 2 mg tablets failed due to tube blocking of smaller tubes (e.g. 8 Fr). This information is relevant for alternative administration of Olumiant 2 mg tablets.

The dispersion and rinse volumes for each administration route are appropriately justified in terms of dose delivery.

The question raises whether a relatively significant difference between 5 or 10 minutes tablet dispersion time could have an impact on tube blocking, especially for the nasogastric/orogastric administration through smaller tubing. The MAH is asked to clarify this since the worst-case dispersion times could not be deduced from the experimental data. If necessary, a minimum dispersion time instead of a range should be established for the NG/OG administration.

The product information is established as per the EMA Q&A on 'Administration of oral immediate release medicinal products through enteral feeding tubes, Section 2. What should be in the SmPC and PIL?'

2.3. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

2.3.1. Ecotoxicity/environmental risk assessment

Summary of Environmental Risk Assessment for the Use of Baricitinib in Europe

Baricitinib was approved in the European Union in 2017 for the treatment of moderate to severe rheumatoid arthritis and in 2020 for the treatment of moderate to severe atopic dermatitis. An environmental risk assessment (ERA) was submitted as part of the initial marketing authorisation and the following extension of indication (atopic dermatitis, alopecia areata). The current application is to

extend the indication for the use of baricitinib for the treatment of coronavirus disease 2019 (COVID-19). An updated environmental risk assessment is provided that considers a total environmental exposure due to all uses of baricitinib.
Since the environmental data package with baricitinib has not changed since the atopic dermatitis approval and because the use for the COVID-19 indication in hospitalized patients for up to 14 days increases the predicted environmental concentrations by less than 3%, this ERA has been abbreviated to expediate review for this indication. Details on the determination of the separate study results can be found in the Rheumatoid Arthritis Marketing Authorisation Application (EMEA/H/C/004085/0000) and the Atopic Dermatitis Extension of Indication (EMEA/H/C/004085/II/0016).
Data from environmental chemistry, fate and toxicity studies and predictions of concentrations in the environment were considered to evaluate the risk to the environment from the therapeutic use of baricitinib in humans in Europe. Using assumptions of no metabolism, no removal during sewage treatment, and considering all indications of baricitinib (rheumatoid arthritis, atopic dermatitis, and COVID-19), the maximum predicted environmental concentrations (PEC) of baricitinib residue in the sewage treatment plant, surface water, groundwater, and sediment are 0.408 µg/L, 0.0408 µg/L, 0.0102 µg/L, and 156 µg/kg (dry weight), respectively.
The predicted no-effect concentrations (PNECs) of baricitinib for surface water, sewage microorganisms, and groundwater are 60 µg/L, 100,000 µg/L and 210 µg/L, respectively. The PNEC for sediment was 27,150 µg/kg. The predicted environmental concentrations of total residues of baricitinib are significantly lower than the PNEC values. Therefore, excretion by humans of baricitinib and its metabolites is not expected to result in a significant environmental risk to aquatic organisms.
Baricitinib is not expected to bioaccumulate in aquatic organisms and it does not meet the criteria for classification as a toxic. Therefore, baricitinib is not classified as persistent, bioaccumulative and toxic (PBT) or a very persistent/very bioaccumulative (vPvB) molecule.

Use of Baricitinib

Baricitinib is a selective inhibitor of the Janus kinase (JAK) family of tyrosine kinases. Baricitinib is currently registered to treat the inflammatory diseases rheumatoid arthritis, atopic dermatitis and alopecia areata at doses of 2 or 4 mg per day. Approval of a new indication, patients with COVID-19, is now being requested.

Phase I Environmental Risk Assessment

To conduct the Phase I environmental risk assessment for baricitinib, the EMA guideline for Environmental Risk Assessment of Medicinal Products for Human Use (CHMP 2006) and the Questions and Answers (Q&A) on the guideline (EMA 2016) were consulted to calculate an initial estimate of the predicted surface water concentration (PECsurface water, PECsw) and screen for persistence, bioaccumulation and toxicity.

Screen for Persistence, Bioaccumulation and Toxicity

The log Kow of baricitinib has been empirically measured at pH values of 5, 7, and 9 and was found to range from 1.38 to 1.50. Since the log Kow value is less than 4.5, baricitinib is not considered to be a PBT or a vPvB compound.

Estimate of PECsurface water

Since baricitinib will be used to treat multiple indications, the PECsurface water is calculated for each indication and then summed. The PECsurface water is based on the maximum recommended daily dose of the active ingredient, 200 L of wastewater discharge per capita, an average dilution factor of 10 for discharge into surface water, and the percent of the population assumed to receive the drug product:

$$PEC_{surface\ water} = \frac{DOSE_{ai} \times F_{pen}}{WasteW_{inhab} \times DILUTION \times 100}$$

Where:

- DOSEai = maximum recommended daily dose of active ingredient (4 mg)
- Fpen = percent of population receiving baricitinib (default assumption of 1% or refined value)
- $WasteW_{inhab}$ = amount of wastewater discharged per person in a population per day (assumed to be 200 L)
- DILUTION = surface water dilution (assumed to be 10)

For rheumatoid arthritis and atopic dermatitis, the default Fpen (fraction of the population receiving baricitinib) value of 1% was assumed for each indication. Question 4 of the Q&A (EMA 2016) document allows for refinement of Fpen for indications that have a well-defined treatment regimen, such as the 14-day treatment duration for COVID-19. Therefore, the default Fpen of 1% was adjusted to 0.038% based on the treatment regimen for COVID-19 (1% × 14 days ÷ 365 days = 0.038%). The initial estimate of the PECsurface water for baricitinib is 0.0408 µg/L. Since it is greater than 0.01 µg/L, a Phase II environmental risk assessment was conducted.

Table 1 ***Phase I Estimated PECsurface water for Baricitinib***

Indication	**Default or Refined F_{pen}**	**$PEC_{surface\ water}$**
Rheumatoid arthritis	1%	0.02 µg/L
Atopic Dermatitis	1%	0.02 µg/L
COVID-19	0.038%	0.0008 µg/L
Summary of PEC_{SW} for all indications		**0.0408 µg/L**

Abbreviations: PEC = predicted environmental concentration; Fpen = percent of the population receiving baricitinib.

Phase II Environmental Risk Assessment

The Phase II environmental risk assessment for baricitinib was conducted in compliance with the EMA guideline for environmental risk assessment of medicinal products for human use (CHMP 2006). An environmental dataset of physical-chemical properties, degradation studies, and acute and chronic toxicity studies with aquatic organisms was collected with baricitinib. The results of these studies support an understanding of the distribution and fate in the environment and allows calculation of PNEC for various environmental compartments. The PNECs were compared to the PECs to evaluate the risk of baricitinib to aquatic organisms. The results of the environmental studies are included in the summary tables below.

Predicted Environmental Concentrations

Surface Water

The PECsurface water calculated in the Phase I assessment will be used (0.0408 µg/L). For perspective, the PECsurface water for rheumatoid arthritis and atopic dermatitis only is 0.04 µg/L; the addition of the COVID-19 indication increases the surface water PEC by only 2%.

Sewage Treatment Plant

The concentration of baricitinib in the sewage treatment plant is calculated using the same assumptions as the surface water calculation (see Estimate of PECsurface water) but without the ten-fold dilution and is, therefore, 0.408 µg/L.

Sewage Sludge and Soil

The Koc of baricitinib for sewage sludge is less than 10,000, therefore, the transfer of baricitinib to the

terrestrial compartment via binding to sewage sludge solids and subsequent application to land is not expected to result in significant concentrations that are harmful to the environment.

Groundwater

The guideline for environmental risk assessment (CHMP 2006) suggests that for substances with an estimated Koc of less than 10,000, transfer to groundwater is primarily through bank filtration and can be simply estimated as 25% of the PECsurface water (0.0408 µg/L × 0.25 = 0.0102 µg/L).

Sediment

The concentration in sediment can be predicted using the maximum surface water concentration and the measured Koc values for soil using equilibrium partitioning to suspended matter as described in the REACH guidance (ECHA 2016, see calculations in Appendix A of the ERA document). The PECsediment is calculated to be 156 µg/kg considering all three indications. Since the PECsediment for only rheumatoid arthritis and atopic dermatitis was 152 µg/kg, the addition of the COVID-19 indications increases PECsediment by only 2.6%.

Summary of Predicted Environmental Concentrations

Table 2 ***Phase II Predicted Environmental Concentrations***

Compartment	**PEC**
Sewage Treatment Plant (PECsewage treatment plant)	0.408 µg/L
Surface Water (PECsurface water)	0.0408 µg/L
Sediment (PECsediment)	156 µg/kg
Groundwater (PECgroundwater)	0.0102 µg/L

Abbreviation: PEC = predicted environmental concentration.

Calculation of Predicted No Effect Concentrations

Predicted No-Effect Concentration (PNEC) values were derived for each compartment using the no-observed-effect concentration (NOEC) for the most sensitive species and respective assessment factors as described in the Rheumatoid Arthritis Marketing Authorisation Application and the Atopic Dermatitis Extension of Indication.

Table 3 ***Phase II Predicted No-Effect Environmental Concentrations***

Environmental Compartment	**Most Sensitive Species**	**NOEC**	**Assessment Factor**	**PNEC**
Sewage Treatment Plant	Microorganisms	1,000,000 µg/L	10	100,000 µg/L
Surface Water	Fish	600 µg/L	10	60 µg/L
Sediment	Midge	2,715,000[a] µg/kg	100	27,150 µg/kg
Groundwater	Daphnia	2100 µg/L	10	210 µg/L

Abbreviations: NOEC = no-observed-effect concentration; PNEC = predicted no-effect concentration.
[a] Adjusted for organic carbon content of a standard sediment.

Fate and Effects Analysis

Table 4 ***PEC/PNEC ratios for Baricitinib***

Environmental compartment	Maximum PEC	PNEC	PEC/PNEC
Surface water	0.0408 µg/L	60 µg/L	0.0007
Sediment	156 µg/kg	27,150 µg/kg	0.006
Surface water (microorganism)	0.0408 µg/L	100,000 µg/L	0.0000004
Ground water	0.0102 µg/L	210 µg/L	0.00005
Sewage Treatment Plant (microorganism)	0.408 µg/L	100,000 µg/L	0.000004

Abbreviations: PEC = Predicted Effect Concentration; PNEC = Predicted No Effect Concentration.

Using the maximum predicted environmental concentrations of baricitinib summed for all indications (rheumatoid arthritis, atopic dermatitis, and COVID-19), all PEC/PNEC ratios are considerably less than 1; that is, the maximum exposures to baricitinib in the environment are much lower than any concentration that is expected to have environmental impacts. Therefore, it is extremely unlikely that baricitinib and its metabolites are a risk to the aquatic environment or the microbial population in sewage treatment plants.

Physical-chemical properties and results from degradation studies indicate that baricitinib will disappear slowly over time from water due to degradation and become unavailable due to sorption to sediment. Baricitinib is not expected to bioaccumulate in aquatic organisms given its Kow of less than 1000. Based on the Koc of baricitinib, significant transfer to the terrestrial environment is not expected. While baricitinib could persist in sediments, it is unlikely that it will build up over time due to its water solubility and equilibrium with surface water. Concentrations expected in sediments would be far below the concentrations evaluated in this assessment that resulted in no effects in sediment-dwelling invertebrates. Therefore, even though baricitinib has the potential to persist in the sediment compartment, it is not expected to pose a significant risk.

PBT Evaluation

Baricitinib does not meet the ECHA criterion for bioaccumulative because its log Kow value is not greater than 4.5 (ECHA 2017). Additionally, baricitinib does not meet the criterion for toxic to aquatic organisms because the long-term NOEC is not less than 10 µg/L and it does not meet the criteria for toxic based on carcinogenicity, mutagenicity, and reproductive toxicity as defined in ECHA (2017). Therefore, baricitinib is not classified as a PBT or vPvB molecule.

Conclusion

Data from environmental chemistry, fate and toxicity studies and predictions of concentrations in the environment were considered to evaluate the risk to the environment from the therapeutic use of baricitinib in humans in Europe. Using assumptions of no metabolism, no removal during sewage treatment, and considering the use of baricitinib for rheumatoid arthritis, atopic dermatitis, and COVID-19, the maximum predicted environmental concentrations of total baricitinib residue in the sewage treatment plant, surface water, groundwater, and sediment are 0.408 µg/L, 0.0408 µg/L, 0.0102 µg/L, and 156 µg/kg (dry weight), respectively.

The PNECs of baricitinib for surface water, sewage microorganisms, and groundwater are 60; 100,000; and 210 µg/L, respectively. The PNEC for sediment was 27,150 µg/kg. The predicted environmental concentrations of total residues of baricitinib are significantly lower than the PNEC values. Therefore, excretion by humans of baricitinib and its metabolites is not expected to result in a significant environmental risk to aquatic organisms.

Baricitinib is not expected to bioaccumulate in aquatic organisms and it does not meet the criteria for classification as a toxic. Therefore, baricitinib is not classified as a PBT molecule.

Summary of main ERA study results (including updated PECsw)

Substance (INN/Invented Name): baricitinib					
CAS-number (if available): 1187594-09-7					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	1.4 (pH 5) 1.4 (pH 7) 1.5 (pH 9)			Potential PBT (N)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	1.4 (pH 5) 1.4 (pH 7) 1.5 (pH 9)			not B
	DT50	DT_{50} water: 22.8 / 50.7 d DT_{50} system 349 / 279 d			Results obtained in two river systems; DT_{50} values corrected to 12°C. Conclusion: vP
Toxicity	NOEC algae NOEC crustacea NOEC fish	3.1 mg/L 2.1 mg/L 0.6 mg/L			not T
	CMR	toxicity to reproduction observed			potentially T
PBT-statement :	baricitinib is not PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surface\ water}$, default F_{pen}	0.041	µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)					(N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} = 16 952 L/kg (soil) K_{oc} = 13 250 L/kg (soil) K_{oc} = 36 083 L/kg (soil) K_{oc} = 371 L/kg (sludge) K_{oc} = 276 L/kg (sludge)			Geomean used in risk assessment: $K_{oc,soil}$ of 20 087 L/kg, and $K_{oc,sludge}$ of 320 L/kg.
Ready Biodegradability Test	OECD 301				Not available, but can be waived because OECD 308 is submitted.
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	DT_{50} water: 10.8/24.0 d DT_{50} system 165/132 d Compound shifts to sediment, 38-47% over the duration of the test			Results obtained in two river systems; sediment risk assessment triggered
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Pseudokirchenriella subcapitata*	OECD 201	NOEC	3100	µg/L	growth rate
Daphnia sp. Reproduction Test	OECD 211	NOEC	2100	µg/L	mortality and reproduction
Fish, Early Life Stage Toxicity Test/*Pimephales promelas*	OECD 210	NOEC	600	µg/L	growth
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	$\geq 10^6$	µg/L	respiration

Phase IIb Studies					
Sediment dwelling organism/*Chironomus riparius*	OECD 218	NOEC	≥2570	mg/kg	normalised to 10% o.c.

2.3.1. Discussion on non-clinical aspects

During the initial procedure at MAA (EMEA/H/C/004085), a full ERA of baricitinib was submitted, including the determination of physical-chemical properties, Phase I and II fate studies. Upon the inclusion of the atopic dermatitis (AD) indication during the type II procedure (EMEA/H/C/004085/II/0016), the ERA was updated (a.o. PECsw) to include the added AD indication.

The MAH has now, based on the current application, recalculated the PECsw, using an Fpen for the extended indication, which is refined based on treatment regime, which is agreed. Therefore, the PECsw slightly increased from 0.04 µg/L to 0.041 µg/L. The new PECsw exceeds the Phase I action limit of 0.01 µg/L. However, as this was already the case at the initial (first) indication at MAA, no additional ERA studies have to be performed. In addition, the other PEC parameters, like ground water, sediment and sewage treatment plant, slightly increased but this did not lead to a different conclusion (PEC/PNEC ratio's <<1) on the low environmental risk of the use of baricitinib. Therefore, the initial conclusion as stated above is maintained.

Baricitinib is neither PBT nor vPvB.

Considering the above data and the environmental risk assessment, baricitinib is not expected to pose a risk to the surface water and groundwater compartment and the sewage treatment plant.

2.3.2. Conclusion on the non-clinical aspects

Considering the above data, baricitinib is not expected to pose a risk to the environment.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 5 Tabular overview of clinical studies

Study	Type of study	Population (N)	Study design and type of control	Treatments	Study status
ACTT-2	Efficacy, Safety	1033 Baricitinib + remdesivir (n=515) Placebo + remdesivir (n=518)	Randomized, double-blind, placebo controlled, parallel group clinical trial in hospitalized COVID-19 patients	Baricitinib 4 mg oral, dosed 14 days or Placebo. All patients received Remdesivir (10 days): Remdesivir 200 mg IV Day 1: Followed by 100 mg IV QD Days 2-10	Completed
KHAA/COV-BARRIER	Efficacy, Safety	1525 Baricitinib + SOC (n=764) Placebo + SOC (n=761)	Randomized, double-blind, placebo controlled, parallel group clinical trial in hospitalized COVID-19 patients	Baricitinib, 4 mg oral dosed for 14 days on standard of care background treatment	Ongoing

During the third round of this procedure, topline results of the baricitinib arm of the RECOVERY trial were provided at the CHMP'Ss request. The RECOVERY trial is a randomised, controlled, open-label platform trial, assessing multiple possible treatments in patients hospitalised for COVID-19.

2.4.2. Pharmacokinetics

At the original MAA for the treatment of moderate to severe rheumatoid arthritis, the pharmacokinetics of baricitinib were investigated in 27 clinical *in vivo* PK studies after single (1-40 mg) or repeated dosing (up to 20 mg once daily for 10 days, up to 15 mg once daily for 28 days, and up to 10 mg daily for 28 days). In addition, several *in vitro* studies with human biomaterials were provided investigating the protein binding, metabolism, and the potential for baricitinib to cause DDIs. Three additional clinical PK studies were performed in patients with atopic dermatitis for the line-extension for the treatment of patients with atopic dermatitis.

To support the present application, one PK study in adult COVID-19 patients on mechanical ventilation was performed (study **KHAA**).

Table 6 Clinical PK studies

study	description	dosing regimen
new PK studies		
KHAA	multiple dose efficacy and safety in adult patients with COVID-19 (n=30)	4 mg once daily as a solution of crushed tablets administered via naso-gastral tube
PK studies in healthy subjects		
JADF	single dose safety and tolerability, PK, PD	fasted: 1, 2, 5, and 10 mg fed: 5 mg
JADE	multiple dose safety, PK, PD	Part 1: dosed for 10 days once daily with 2, 5 or 10 mg or twice daily with 5 mg* Part 2: dosed for 28 days once daily with 10 mg or twice daily with 5 mg Part 3: once 20 mg at Day 1 and from Day 8 to 18 20 mg once daily
JADO	safety, tolerability, and PK of supra-therapeutic doses	single oral dose of 20, 30, or 40 mg
JADG	^{14}C-baricitinib disposition	unlabelled and ^{14}C labelled drug substance containing 10 mg baricitinib and 100 µCi radioactivity
JAGM	absolute bioavailability and PK	single oral 4 mg dose simultaneously with IV infusion of 4 µg [$^{13}C_4D_3{}^{15}N$]-baricitinib
JADM	single- and multiple-dose safety, PK in Japanes subjects	single dose: 2, 5, 10, or 14 mg multiple dose(10 days): 10 or 14 mg (once daily)
JADF	single dose safety and tolerability, PK, PD	fasted: 1, 2, 5, and 10 mg fed: 5 mg
JADH	PK and relative bioavailability	each subject received the following 4 treatments: • 2 x 4 mg phosphate salt capsules (fasted)

		• 1 x 8 mg free-base tablet with particle size 20 µm (fasted) • 1 x 8 mg free-base tablet with particle size 50 µm (fasted) • 1 x 8 mg free-base tablet with particle size 50 µm (high fat meal)
JAGO	relative bioavailability of commercial tablet to Phase 2 tablet and food effect in Japanese subjects	Each subject received the following 5 treatments: • 2 × 4 mg Commercial Tablets (fasted) • 1 × 4 mg Commercial Tablet (fasted) • 1 × 4 mg Commercial Tablet (low-fat meal) • 1 × 8 mg Phase 2 Tablet (fasted) • 1 × 4 mg Phase 2 Tablet (fasted)

PK studies in patients with rheumatoid arthritis		
JADC	baricitinib vs background therapy	Once daily baricitinib 4, 7 or 10 mg
JADA	placebo-controlled, dose-ranging study in patients on background methotrexate therapy	Part A: baricitinib 1, 2, 4, or 8 mg once daily Part B: baricitinib 2 mg twice daily or baricitinib 2, 4, or 8 mg once daily Part C: baricitinib 4 or 8 mg once daily Part D: baricitinib 4 mg once daily
JADN	placebo-controlled, dose-ranging study in patients on background methotrexate therapy in Japanese subjects	Part A: baricitinib 1, 2, 4, or 8 mg once daily Part B: baricitinib 4 or 8 mg once daily
JADV	baricitinib versus placebo or active control in patients who have had an inadequate response to methotrexate therapy	Part A (0-24 weeks): baricitinib 4 mg once daily Part B (24-52 weeks): baricitinib 4 mg once daily
JADZ	baricitinib versus other in patients who have had limited or no treatment with methotrexate	Group A: baricitinib 4 mg once daily plus methotrexate Group B: baricitinib 4 mg once daily Group C: Methotrexate
JADX	baricitinib versus placebo patients with inadequate response to conventional treatment	Group A: baricitinib 4 mg once daily Group B: baricitinib 2 mg once daily Group C: placebo
JADW	baricitinib versus placebo in patients with inadequate response to TNF inhibitors	Group A: baricitinib 4 mg once daily Group B: baricitinib 2 mg once daily Group C: placebo
PK studies in patients with atopic dermatitis		

JAHG	efficacy and safety in combination with moderate potency topical corticoid steroid	2 mg or 4 mg once daily
JAHL	efficacy and safety	1 mg, 2 mg or 4 mg once daily for 16 weeks
JAHM	efficacy and safety	1 mg, 2 mg or 4 mg once daily for 16 weeks
PK studies in special populations		
JADL	effect of renal impairment on PK, PD, safety and tolerability	Single oral dose Healthy/Mild/Moderate: 10 mg Severe: 5 mg ESRD: 5 mg in 2 study periods separated by a 2-week washout
JAGC	effect of hepatic impairment on PK, safety, and tolerability	single oral 4 mg dose
JADP	efficacy and safety of baricitinib to placebo in subjects with moderate-to-severe psoriasis	Oral dose of 2, 4, 8, or 10 mg
JAGQ	efficacy and safety of baricitinib to placebo in subjects with diabetic kidney disease	Oral dose of 0.5, 0.75, 1, 1.5, 2.75, or 4 mg once daily or 0.5 or 0.75 mg twice daily
DDI studies		
JAGJ	effect of ketoconazole or fluconazole on baricitinib PK in healthy subjects	Period 1: baricitinib single oral 10 mg dose Period 2: baricitinib single oral 10 mg dose on Day 6 of ketoconazole dosing or on Day 7 of fluconazole dosing
JAGK	effect of rifampicin on baricitinib PK in healthy subjects	Period 1: baricitinib single oral 10 mg dose on Day 1 Period 2: baricitinib single oral 10-mg dose on Day 10 of rifampicin dosing
JAGH	effect of cyclosporine on baricitinib PK in healthy subjects	Period 1: baricitinib single oral 4 mg dose

		Period 2: baricitinib single oral 4 mg dose co-administered with cyclosporine on Day 4
JAGG	effect of probenecid on baricitinib PK in healthy subjects	Period 1: baricitinib single oral 4 mg dose Period 2: baricitinib single oral 4 mg dose on Day 3 of probenecid dosing
JAGF	effect of increased gastric pH (omeprazole) on baricitinib bioavailability in healthy subjects	Period 1: baricitinib single oral 10 mg dose Period 2: baricitinib single oral 10 mg dose on 8th day of omeprazole dosing (Day 10)
JADB	effect of methotrexate on baricitinib PK in rheumatoid arthritis patients	weekly dose methotrexate (Days 1, 8, 15, 22), plus once daily baricitinib 10 or 15 mg or twice daily 5 mg (Days 3-28)
JAGI	Effect of baricitinib on PK of simvastatin and simvastatin acid in healthy subjects	Period 1: simvastatin single oral dose Period 2: simvastatin single oral dose on Day 6 of baricitinib dosing (10 mg once daily on Days 3-7).
JAGD	Effect of baricitinib on PK of Microgynon in healthy women taking oral contraceptives	Period 1: Microgynon single oral dose Period 2: Microgynon single oral dose on Day 7 of baricitinib dosing (10 mg once daily for 8 days)
JAGL	Effect of baricitinib on PK of digoxin in healthy subjects	digoxin loading dose followed by once daily dosing on Days 2-7, followed by digoxin + 10 mg baricitinib once daily dosing on Days 8 to 16
JADB	Effect of baricitinib on PK of methotrexate in rheumatoid arthritis patients	weekly dose methotrexate (Days 1, 8, 15, 22), plus once daily baricitinib 10 or 15 mg or twice daily 5 mg (Days 3-28)

* Metabolite identification from the 10 mg once daily dose for 10 days.

Absorption

After oral administration of baricitinib, C_{max} levels are reached ~1h after dosing (0.5-3.0 h). The absolute oral bioavailability of baricitinib from the commercial tablet is ~79% in healthy volunteers.

In healthy volunteers, the C_{max} is ~112 nM and the $AUC_{0-\infty}$ is 740 nM $\times$ h at the clinical dose of 4 mg. In subjects with rheumatoid arthritis, the C_{max} (~135 nM) and AUC_{T} (~1200 nM × h) are higher compared to healthy volunteers. In addition, CL/F is ~46% lower and $t_{½}$ ~25% lower in rheumatoid arthritis patients relative to that in heathy subjects. In patients with atopic dermatitis, the C_{max} and AUC at steady state are 124 nM and 1117 nM × h, respectively, at the clinically relevant dose of 4 mg. The exposure tends to be lower in patients with atopic dermatitis compared to patients with rheumatoid arthritis (factor 0.86) and higher compared to healthy volunteers (not assessed by the MAH) at the clinically relevant dose of 4 mg

A low-fat meal led to a 14% decrease in $AUC_{0-\infty}$ and an 11% decrease in C_{max} in healthy volunteers, which did not lead to a significant effect in the pharmacokinetics of baricitinib. A high-fat meal decreased the AUC with 4-11% and the C_{max} with 10-18% in healthy volunteers. The decrease in C_{max} and AUC is clinically not relevant.

In healthy volunteers, the intra-individual variability in AUC and C_{max} is low (<14%) and the inter-individual variability moderate (17-26%). The inter-individual variability in rheumatoid arthritis patients is higher compared to healthy subjects (41% versus ~22%). The inter-individual variability was 50% for the AUC and 21% for the C_{max} in patients with atopic dermatitis.

The PK of baricitinib was investigated in adult patients with COVID-19 (study **KHAA**) to support the present application. PK samples were obtained at 15 minutes, 1 hour, and any time between 2 to 4 hours post-dose at Day 1 and pre-dose; then 30 minutes, and any time between 6 to 10 hours post dose at Day 3 of intubation. All PK data from study KHAA (246 concentrations from 53 patients) were evaluated via PopPK modelling. The same PopPK model previously developed and applied for the PK analysis for healthy subjects and patients with rheumatoid arthritis and atopic dermatitis was used to describe the concentration-time data in patients with COVID-19. The PopPK model is sufficiently able to estimate the PK in COVID 19 patients from samples obtained in COVID-19 patients. At a 4 mg once daily dose, the $C_{max,ss}$ is 102.8 nM (= 38.2 ng/mL; CV%= 51%) and the $AUC_{T,ss}$ is 880 nM × h (= 327 ng × h/mL; CV%=45%). The exposure in COVID-19 patients are lower than those in the rheumatoid arthritis and atopic dermatitis patients and higher than those in healthy subjects.

Distribution

The plasma protein binding of baricitinib is ~50% and was independent of the concentration (including clinically relevant concentrations). The blood-to-plasma ratio is 1.14, indicating a weak/moderate association with the blood cell compartment.

The volume of distribution is ~1.6 L/kg, indicating that baricitinib distributes from the plasma compartment into tissues. The Vd is 1.2 L/kg in patients with rheumatoid arthritis and 1.4 L/kg in patients with atopic dermatitis. In patients with COVID-19, the volume of distribution is ~1.5 L/kg (using an average body weight of 92.8 kg and a bioavailability of 0.79).

Metabolism

Only baricitinib was detected circulating in human plasma. Metabolites accounted for 4-7% of the dose in urine and ~1% in faeces. In addition, baricitinib is metabolised to a limited extent *in vitro*. Overall, these data indicate that metabolism does not significantly contribute to the clearance of baricitinib. The enzymes involved in the limited metabolism of baricitinib were not identified, but this is also not warranted.

Transporters

In vitro studies indicate that baricitinib is a substrate for P-glycoprotein, BCRP, OAT3 and MATE2-K. Baricitinib is not a substrate for OATP1B1, OATP1B3, OAT1, OCT1, OCT2, and MATE1. The transporters P-glycoprotein, OAT3 and MATE2-K are most likely involved in the active excretion into urine. BCRP may be involved in the excretion into faeces. However, excretion via faeces is limited and therefore the *in vivo* contribution of BCRP in to the excretion of baricitinib is most likely limited. Genetic polymorphisms in P-glycoprotein will most likely not have a clinically relevant effect on the PK of baricitinib. For MATE-2K, a conclusion on whether SNPs in MATE-2K would lead to clinically significant changes in the PK of baricitinib cannot be drawn as current information is too limited. A higher clearance of baricitinib due to the rs12943590 variant in MATE-2K will most likely not lead to a clinically relevant effect since good response was observed in non-renal patients to a 2 mg dose.

Excretion

Baricitinib is mainly excreted via urine and predominately as parent. Around 20% of the dose is excreted via faeces. This is most likely mainly unabsorbed baricitinib since the bioavailability is ~79%. The total clearance is ~21 L/h, and the renal clearance is ~17 L/h in healthy subjects. These results indicate that baricitinib is actively excreted into urine, which is confirmed by the transporter studies. The CL is 11.9 L/h in patients with rheumatoid arthritis and ~14.2 L/h in patients with atopic dermatitis. In patients with COVID-19, the CL is 18.0 L/h. The elimination half-life of baricitinib is ~10 h in healthy volunteers and 12.5 h in patients with rheumatoid arthritis, and 12.9 h in patients with atopic dermatitis.In patients with COVID-19, the elimination half-life is 10.8 h.

Dose proportionality and time dependencies

The C_{max} and $AUC_{0-\infty}$ increase dose-proportional in healthy subjects over a single-dose range of 1 to 30 mg (slightly more over the dose range 30 to 40 mg). The kinetics of baricitinib from the commercial tablet was dose-proportional over 2 to 4 mg.

After multiple once-daily dosing, steady-state was reached between the second and third dose. Accumulation after repeated-dose administration of baricitinib is minimal; the accumulation ratio ranged from 0.89- to 1.25-fold and 1.02- to 1.24-fold based on C_{max} and AUC, respectively.

Special populations

The effect on the pharmacokinetics of baricitinib of renal function, hepatic function, age, weight, race, gender, and Erythrocyte Sedimentation Rate were investigated.

Moderate hepatic impairment, age (age range of 19 to 83 years) and Erythrocyte Sedimentation Rate (a measure of disease state in Rheumatoid Arthritis patients) did not have a clinically significant effect on the exposure to baricitinib. No clinical studies with baricitinib were performed in patients with severe

hepatic impairment. Patients with severe hepatic impairment often have serious co-morbidities, which calls for caution when considering pharmacological treatment. Therefore, the use of baricitinib in patients with severe hepatic impairment is not recommended which is acceptable.

A reduction in baricitinib renal clearance and an increase in the AUC were observed with increased severity of renal impairment. An increase of 4-fold in AUC and 1.4-fold in C_{max} was observed in subjects with severe renal impairment compared to normal renal function following a single dose. In patients with Rheumatoid Arthritis, a less pronounced effect of the renal function on the exposure of baricitinib was observed. This is consistent with a reduced fraction of excretion out of the total elimination pathways of baricitinib in patients with Rheumatoid Arthritis compared to healthy subjects. PopPK modelling was performed to support a change in dosing regimen in patients with COVID-19 and severe renal impairment (a dose of 2 mg every 48 hours). This is an acceptable approach, since the PK of baricitinib is linear over a dose range of 1 to 5 mg and the majority is eliminated as parent via urine. The results of the dedicated renal impairment study were included in the PopPK model. The estimated exposure using this dosing scheme of 2 mg every 48 hours in severe renal impaired subjects appears to be similar compared to healthy volunteers dosed with 4 mg every 24 hours.

In addition, C_{max} decreased with increasing body weight. However, the effect of body weight on baricitinib PK is not considered clinically relevant in adults. Gender and race (American versus Japanese) were shown to have an effect on the PK of baricitinib, but this is most likely due to differences in body weight.

Pharmacokinetic interaction studies

Baricitinib as victim

In vitro and *in vivo* data indicate that >10% of the baricitinib dose is metabolised. Baricitinib is actively excreted by the transporters P-glycoprotein, BCRP, OAT3 and MATE2-K. In clinical Drug Drug Interaction (DDI) studies, the potential of other drugs to affect the PK of baricitinib was investigated. A clinically significant interaction was observed when baricitinib was co-administered with probenecid (a strong OAT3 inhibitor). No other clinical DDI studies have been conducted with OAT3 inhibitors with less inhibition potential. Co-administration of ketoconazole (strong CYP3A inhibition), fluconazole (strong CYP2C19 inhibition and moderate CYP2C9 and 3A inhibition), rifampicin (inducer via CAR/PXR of among others CYP3A and P-glycoprotein) and cyclosporine (P-glycoprotein inhibition) with baricitinib did not have a clinically relevant effect on the pharmacokinetics of baricitinib. No *in vivo* studies were performed for inhibition of BCRP and MATE2-K. Complete inhibition of BCRP may lead to a bioavailability of 100% which may result in an AUC increase of 1.25. This increase is not considered clinically relevant. Furthermore, the clinical significance of an interaction at MATE2-K would be minimal given the multiple exit routes of baricitinib from the proximal tubule cell. Maximal inhibition of MATE-2K will lead to a less than 2-fold increase in AUC of baricitinib, because other transporters can compensate for the lack of function. Therefore, inhibition of MATE-2K is likely not clinically relevant. An increase in gastric pH does not affect the overall exposure to baricitinib. Therefore, baricitinib may be co-administered with drugs that are gastric pH modifying agents.

Baricitinib as perpetrator

Baricitinib is not an inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4, and 3A5 at clinically relevant concentrations. In addition, baricitinib is not an inducer via AhR, PXR and CAR at clinically relevant maximal plasma concentrations, portal vein concentrations and maximal intestinal concentrations. Therefore, it is unlikely that baricitinib will lead to clinically relevant DDIs due to CYP inhibition or induction. Furthermore, baricitinib is not an inhibitor of the transporters P-glycoprotein, BCRP, OATP1B1,

OATP1B3, OCT2, OAT1, OAT2, OAT3, MATE-1 and MATE2-K at clinically relevant concentrations. Baricitinib may be an inhibitor of OCT1 at maximal portal vein concentrations. Concomitant administration of baricitinib with drugs for which the rate-limiting step is hepatic uptake by OCT1, may lead to an increase in C_{max}.

In clinical DDI studies, the potential of baricitinib to affect the PK of oral contraceptives (via CYP3A), simvastatin (via CYP3A and OATP1B1), and digoxin (via P-glycoprotein) was investigated. The clinical DDI studies confirm the *in vitro* data that baricitinib is not an inhibitor or inducer of CYP3A and not an inhibitor of P-glycoprotein. Concomitant administration with simvastatin led to a (not clinically significant) decrease in AUC and C_{max} of simvastatin. The underlying mechanism of action is unknown. Furthermore, baricitinib does not have an effect on the PK of methotrexate, a commonly concomitant prescribed drug, in Rheumatoid Arthritis patients.

In the clinical safety studies, an effect on the creatinine clearance was observed (decrease in creatinine clearance). Creatinine is cleared by the following transporters OCT2, OAT2, MATE1 and MATE2-K. Baricitinib was not an inhibitor of OCT2, OAT2, MATE1 and MATE2-K at clinically relevant concentrations. The cause for this observed decreased creatinine clearance is unknown.

2.4.3. Pharmacodynamics

Mechanism of action

Baricitinib has known anti-inflammatory activity, also described for adult patients with RA (Bronte et al. 2020) and paediatric patients with type 1 interferonopathies (Sanchez et al. 2018; Kim et al. 2020). More recently, baricitinib was shown to reverse dysregulated inflammatory markers in patients with COVID-19 (McInnes et al. 2019; Sims et al. 2021). Relevant to COVID-19 and the known role of increased IL-6 level in patients with severe disease (Herold et al. 2020; Rees 2021), it is notable that treatment with baricitinib 4 mg resulted in reduced plasma levels of IL-6 in hospitalised patients with COVID-19, a finding that was replicated after being observed in patients with RA (Bronte et al. 2020; Stebbing et al. 2020; Sims et al. 2021). Furthermore, plasma markers dysregulated in moderate to severe hospitalised patients with COVID-19 represent myeloid dysregulation, endothelial, and cardiovascular inflammation, along with reduced antigen-presenting plasmacytoid dendritic cells normalised over time with baricitinib treatment (Sims et al. 2021).

Baricitinib reduces levels of cytokines and biomarkers implicated in COVID-19, including IL-6, IFN-γ, MCP-3, CXCL10, IL-10, MCP-2, CCL19, PTX3, and IL-27. In addition, markers that are decreased in moderate to severe COVID-19 patients were increased in response to baricitinib and include CCL17, GDF2, and SCF (Sims et al., 2021).

Members of the NAK family of enzymes in humans (AAK1, GAK, BIKE, and STK16) activate the AP-2 scaffolding protein critical for SARS-CoV-2 viral entry and propagation. Baricitinib has now been shown in in vitro assays to inhibit AAK1, BIKE, and GAK with nanomolar affinities (Stebbing et al. 2020). The impact of this antiviral host activity in patients with COVID-19 is being evaluated through the collection of nasopharyngeal swabs, serum, and whole blood for RNA, epigenetic analysis, and cellular phenotyping in the ongoing randomised Study KHAA.

Increases in IgG antibodies against the S1/S2 antigens of SARS-CoV-2 were observed in a limited sample of moderate to severe hospitalised COVID-19 patients treated with baricitinib (Stebbing et al. 2020). This is consistent with published reports on the mechanism of action of baricitinib in influencing the adaptive immune response to antigen challenge (Winthrop et al. 2019).

In conclusion, baricitinib blocks multiple cytokine pathways implicated in COVID-19 pathogenesis. The addition of confirmatory, preclinical supportive data describing the potential antiviral host activity of baricitinib (baricitinib is a potent AAK1/BIKE/GAK inhibitor) complements the known anti-inflammatory effects of baricitinib. Patients could achieve seroconversion (generate neutralising antibodies against the SARS-CoV-2 spike proteins) after baricitinib exposure. These observations provided the rationale to study baricitinib in the context of randomised, controlled clinical trials in patients with COVID-19 infection.

CHMP's comment

Whilst the information provided by the MAH is acknowledged, no preclinical data has been submitted in support of the hypothesized MoA in patients with COVID-19. The lack of preclinical data for the current EoI to include treatment of COVID-19 could be considered acceptable if the clinical benefit observed in the pivotal trial is deemed sufficiently robust.

Primary and secondary pharmacology

The clinical pharmacology of baricitinib has previously been evaluated in the marketing authorisation application for RA and subsequent extension of indications (atopic dermatitis, alopecia areata) in the EU.

2.4.4. PK/PD modelling

The MAH proposes 2 mg dose once every 48 hours in patients with estimated glomerular filtration rate (eGFR) between 15 mL/min/1.73 m^2 and less than 30 mL/min/1.73 m^2 to allow patients with severe renal dysfunction to gain access to the treatment once the individual risks and potential benefits have been evaluated by the healthcare provider. This is especially important in the treatment of COVID-19 because of the high incidence of acute kidney injury in this population; which may be as high as 20% (Nadim et al. 2020). Patients with eGFR <30 mL/min/1.73 m^2 were excluded from studies ACTT-2 and KHAA. The proposed dosing regime is based on the renal impairment study JADL and PopPK modeling with PK data in adult patients with COVID-19 from study KHAA.

Dedicated renal impairment study JADL

Effects of severe renal dysfunction with baricitinib treatment was previously evaluated in the dedicated renal impairment Study JADL. Study JADL included adult subjects with normal renal function, and with mild, moderate, severe renal dysfunction, and end-stage renal disease. The complete Study JADL data were submitted as part of the initial MAA for baricitinib. Data available from study JADL showed that patients with eGFR 15 to <30 mL/min/1.73 m^2 are associated with an increase in the AUC by approximately 4-fold, with minimal impact on the maximum observed drug concentration (1.4-fold) of baricitinib (Table 7). Accordingly, a dose of 2 mg given every 48 hours in patients with severe renal dysfunction will produce a daily average exposure similar to that of a dose of 4 mg given daily in patients with normal renal function, since the total exposure over a 48-hour interval is the same for the 2 dosing scenarios.

Table 7 Summary of baricitinib plasma pharmacokinetic parameters and geometric mean ratios (reference = healthy cohort) (Pharmacokinetic population) – Study I4V-MC-JADL

Parameter (unit)	Renal Function	Dose (mg)	N	Mean ± SD (Geometric Mean)	Ratio of Dose-Normalized Geometric Means (90% CI)[a,b]
$AUC_{(0-\infty)}$ (ng h/mL)	Normal	10	10	579 ± 121 (568)	
	Mild	10	10	828 ± 208 (802)	1.41 (1.15-1.74)
	Moderate	10	10	1330 ± 472 (1260)	2.22 (1.81-2.73)
	Severe	5	8	1170 ± 241 (1150)	4.05 (3.25-5.03)
C_{max} (ng/mL)	Normal	10	10	85.8 ± 20.2 (82.5)	
	Mild	10	10	102 ± 39.4 (95.8)	1.16 (0.92-1.45)
	Moderate	10	10	123 ± 21.6 (121)	1.46 (1.17-1.83)
	Severe	5	8	60.9 ± 18.8 (58.3)	1.40 (1.11-1.78)

Abbreviations: $AUC_{(0-\infty)}$ = area under the concentration versus time curve from zero to infinity; C_{max} = maximum observed drug concentration; MDRD-GFR = modification of diet in renal disease e-estimated glomerular filtration rate; N = number of subjects analysed.

a Dose-dependent parameters (C_{max} and AUC) were dose-normalised prior to statistical comparisons.

b Ratio of dose-normalised geometric means of Other Group: Normal Group.

Notes: The MDRD- GFR was calculated as:

GFR (mL/min/1.73 m^2) = $175 \times Pcr^{-1.154} \times age^{-0.203} \times 0.742$ (if female) $\times$ 1.210 (if African American)

Subjects with mild renal impairment: MDRD-GFR = 60 mL/min to 89 mL/min

Subjects with moderate renal impairment: MDRD-GFR = 30 mL/min to 59 mL/min

Subjects with severe renal impairment: MDRD-GFR = 15 mL/min to 29 mL/min

PK modelling based on data in patients with COVID-19

A PopPK modelling analysis was conducted based on data in patients with COVID-19 from study KHAA. Consistent with previous findings, renal function also had an impact on the PK in patients with COVID-19. The magnitude of effect of renal function on the PK of baricitinib in patients with COVID-19 was evaluated using the model. Table 8 summarizes the estimated mean ratios (lower eGFR:normal renal function) for area under the concentration-time curve during 1 dosing interval at steady-state ($AUC_{\tau,ss}$) and maximum observed drug concentration during a dosing interval at steady-state ($C_{max,ss}$) in patients with COVID-19 and renal impairment. The baseline eGFR range is 31.0 to 207 mL/min/1.73m^2 in Study KHAA and the PK model was used to predict the exposures for patients with severe renal impairment. The estimated mean AUC ratio is 3.03 (90% CI=2.25-4.51) for patients with severe renal impairment.

Table 8 Estimated mean rations of AUCτ, ss and Cmax,ss for mild, moderate and severe renal impairment in patients with Covid-19

Renal Impairment Group	eGFR[a] (mL/min/1.73 m^2)	Mean Ratio[b] (90% CI) for $AUC_{\tau,ss}$	Mean Ratio[b] (90% CI) for $C_{max,ss}$
Mild	60-<90	1.51 (1.11-2.27)	1.08 (0.820-1.46)
Moderate	30-<60	2.12 (1.51-3.22)	1.19 (0.902-1.55)
Severe	15-<30	3.03 (2.25-4.51)	1.37 (1.05-1.76)

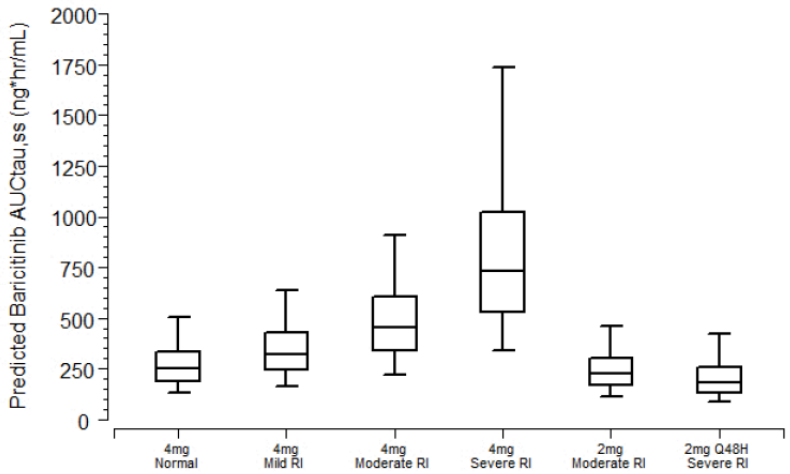
Abbreviations: $AUC_{\tau,ss}$ = area under the concentration-time curve during 1 dosing interval at steady-state; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; $C_{max,ss}$ = maximum observed drug concentration during a dosing interval at steady-state; eGFR = estimated glomerular filtration rate.

a Calculated using the CKD-EPI equation.

b Ratio of lower eGFR: normal renal function.

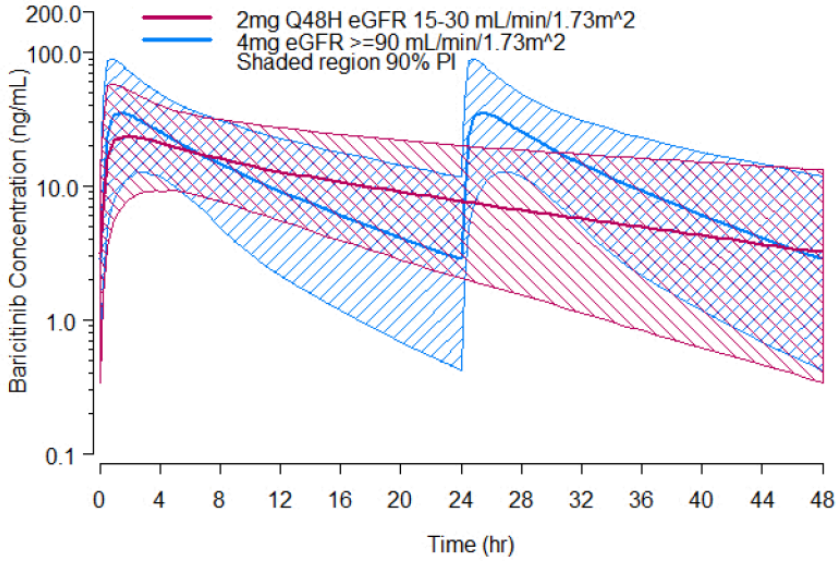
Estimates for $AUC_{T,SS}$ for patients with mild, moderate, and severe renal impairment who received baricitinib 4 mg once daily are compared to those for patients with normal renal function using the PK model in patients with COVID-19 (Figure 1). The graph shows that, when the dosing regimen was changed from 4 mg QD to 2 mg given every 48 hours for patients with severe renal impairment, the resulted exposure ($AUC_{T,SS}$) was comparable to the exposure of patients with normal renal function dosed at 4 mg once daily. Therefore, a dose of 2 mg given every 48 hours for patients with severe renal impairment (eGFR = 15 to <30 mL/min/1.73 m^2) is considered appropriate to provide adequate exposure and ensure patient safety. The PK profiles of patients with COVID-19 with severe renal impairment receiving 2 mg every 48 hours are compared with those in COVID-19 patients with normal renal function receiving 4 mg once daily in Figure 2.

Figure 1 Box plots comparing baricitinib plasma $AUC_{T,SS}$ with various dosing regimens for different renal function groups based on PopPK modelling with data from patients with COVID-19.



Abbreviations: $AUC_{tau,ss}$ = area under the concentration-time curve during 1 dosing interval at steady-state; PK = pharmacokinetic; PopPK = population PK; RI = renal impairment.
Note: Boxes are 25th, 50th, and 75th percentiles; whiskers are fifth to 95th percentiles. Values for the box for 2 mg Q48h for Severe RI were divided by 2 for a comparison to the QD dosing regimens.

Figure 2 Comparing pharmacokinetic profiles following 4 mg once daily in adult subjects with normal renal function and following 2 mg every other day in adult subjects with severe renal impairment.



Abbreviations: hr = hours; eGFR=estimated glomerular filtration rate; PI = prediction interval; PK = pharmacokinetics.
Note: The blue line and band are predicted mean PK profile with 90% PI for 4 mg once daily in patients with normal renal function; the red line and band are predicted mean PK profile with 90% PI for 2 mg given every 48 hours in patients with severe renal impairment.

Treatment-emergent adverse events according to eGFR in patients with COVID-19

Although patients with eGFR <30 mL/min/1.73 m^2 were excluded from Studies ACTT-2 and KHAA, patients with mild (60⩽ eGFR <90) and moderate (eGFR 30 to 60 mL/min/1.73 m^2) baseline eGFR were included. The number of patients included with normal, mild (60⩽ eGFR <90) and moderate (eGFR 30 to 60 mL/min/1.73 m^2) baseline eGFR is presented in Table 9. The table depicts treatment-emergent adverse events (TEAEs) occurring in ⩾2% in any group by preferred term according to baseline eGFR. No consistent pattern or clinically meaningful differences are noted to disfavour baricitinib use in patients with mild and moderate decreases in renal function.

Table 9 Treatment-Emergent Adverse Events occurring in ≥ 2% in any group by preferred term based on baseline eGFR safety population baricitinib Covid-19 PC analysis set (studies ACTT-2 and KHAA)

Preferred Term Baseline eGFR	PBO (N=1261) n (%)	BARI 4-mg (N=1257) n (%)	BARI 4-mg vs. PBO OR 95% CI(a)	 p-value (b)
Normal, Ns	580	571		
Mild, Ns	426	413		
Moderate, Ns	148	146		
Missing, Ns	106	127		
Patients with >=1 TEAE				
Normal	239 (41.2)	227 (39.8)	0.9 (0.7, 1.2)	0.616
Mild	201 (47.2)	183 (44.3)	0.9 (0.7, 1.2)	0.397
Moderate	90 (60.8)	86 (58.9)	0.9 (0.6, 1.5)	0.744
p-value(c)				0.955
Hyperglycaemia				
Normal	32 (5.5)	22 (3.9)	0.7 (0.4, 1.2)	0.181
Mild	21 (4.9)	23 (5.6)	1.1 (0.6, 2.1)	0.688
Moderate	9 (6.1)	6 (4.1)	0.7 (0.2, 1.9)	0.447
p-value(c)				0.462
Glomerular filtration rate decreased				
Normal	21 (3.6)	29 (5.1)	1.4 (0.8, 2.6)	0.215
Mild	16 (3.8)	16 (3.9)	1.0 (0.5, 2.1)	0.973
Moderate	6 (4.1)	4 (2.7)	0.7 (0.2, 2.5)	0.547
p-value(c)				0.509

Abbreviations: N = number of patients in the analysis population; n = number of patients in the specified category;
Ns = number of patients in each subgroup; OR = Mantel-Haenszel odds ratio.
Percentages are based on the number of patients by subgroup in each treatment group (Ns). Preferred terms are sorted in decreasing frequency in the BARI 4-mg group.
PBO and BARI 4-mg groups includes RDV from ACTT-2.
Placebo patient in ACTT-2 is excluded from the summary because baseline eGFR = 27 mL/min/1.73m2.

2.4.5. Discussion on clinical pharmacology

Pharmacokinetics

The MAH is requesting a new indication for the treatment of coronavirus disease 2019 (COVID 19) in hospitalised adult and paediatric patients aged 10 years and older who require low-flow oxygen or non-invasive ventilation/high flow oxygen. During the evaluation, the MAH has restricted the indication claim to adult only (see 5.5.).

A higher apparent volume of distribution (V/F) and lower exposure was observed in COVID-19 patients compared to healthy volunteers and patients with rheumatoid arthritis and atopic dermatitis. This is most likely due to a higher body weight of the COVID-19 patients, included in the studies, as compared to the other studied populations: mean body weight is 92.8 kg for COVID-19, and 73.3 kg, 74.5 kg, and 70 kg for rheumatoid arthritis patients, atopic dermatitis patients, and healthy subjects, respectively. The assumption of the Applicant is that similar exposure in COVID-19 patients leads to a similar safety profile as observed in healthy volunteers and patients with atopic dermatitis and rheumatoid arthritis. The observed exposure in COVID-19 patients was lower than that observed in patients with rheumatoid arthritis and atopic dermatitis and therefore no additional safety issues are to be expected. Therefore, the proposed dosing regimen of 4 mg once daily could be acceptable.

The MAH proposes a different dosing regimen (2 mg every 48 hours) in severe renal impairment (currently not recommended in the other indications) using PopPK modelling to support the dosing recommendation. The modelling showed that the exposure in patients with severe renal impairment dosed with 2 mg every 48 hours is similar to that in healthy volunteers dosed with 4 mg every 24 hour. At the CHMP's request, the MAH revised the dosing recommendations in Section 4.2 of the SmPC as follows:

"*4.2. Posology and method of administration*

Olumiant should only be used in patients with estimated glomerular filtration rate (GFR) between 15 and 30 mL/min if the potential benefit outweighs the potential risk. The recommended dose in patients with estimated GFR between 15 and 30 mL/min is 2 mg once every 48 hours."

This was considered acceptable to the CHMP.

Pharmacodynamics

No new PD data has been submitted. The MAH states that baricitinib blocks multiple cytokine pathways implicated in COVID-19 pathogenesis. The addition of confirmatory, preclinical supportive data describing the potential antiviral host activity of baricitinib (baricitinib is a potent AAK1/BIKE/GAK inhibitor) complements the known anti-inflammatory effects of baricitinib. These observations provided the rationale to study baricitinib in the context of randomised, controlled clinical trials in patients with COVID-19 infection.

Whilst the MAH's rationale is acknowledged, no preclinical data has been submitted in support of the hypothesized MoA in patients with COVID-19. The lack of preclinical data to support the current application could be considered acceptable if the clinical benefit observed in the pivotal trial is deemed sufficiently robust.

2.4.6. Conclusions on clinical pharmacology

Pharmacokinetics

The exposure in COVID-19 patients is lower than those in the rheumatoid arthritis, atopic dermatitis and alopecia areata patients and higher than those in healthy subjects. Therefore, the proposed dosing regimen of 4 mg once daily could be acceptable.

Furthermore, the exposure in severe renal impaired subjects dosed with 2 mg every 48 hours appears to be similar compared to healthy volunteers dosed with 4 mg every 24 hours. Hence, the MAH's proposal dosing regimen of 2 mg every 48 hours in severe renal impairment is acceptable to the CHMP.

Pharmacodynamics

No preclinical data has been submitted in support of the hypothesized MoA in patients with COVID-19. The lack of preclinical data to support the current application could be considered acceptable if the clinical benefit observed in the pivotal trial is deemed sufficiently robust.

2.5. Clinical efficacy

2.5.1. Dose-response studies

No dose-response studies have been performed by the MAH. The intended dose is the currently approved dose of 4mg once daily.

CHMP's assessment Use of the currently registered dose in the pivotal trials is considered acceptable.

2.5.2. Main studies

ACTT-2

Methods

This study is part of an ongoing, adaptive, randomized, placebo-controlled trial to evaluate the efficacy of different investigational therapies in hospitalized patients with COVID-19 (Adaptive COVID Treatment Trial, ACTT). The study is an international, multicentre trial that will be conducted in up to approximately 100 sites globally. New arms can be introduced according to scientific and public health needs. There will be interim monitoring to allow early stopping for futility, efficacy, or safety. If one therapy proves to be efficacious, then this treatment may become the control arm for comparison(s) with new experimental treatment(s). An independent Data and Safety Monitoring Board (DSMB) will actively monitor interim data in all stages to make recommendations about early study closure or changes to study arms.

ACTT-1 (part 1 of the trial) evaluated safety and efficacy of remdesivir as compared to placebo in the treatment of patients with COVID-19. ACTT-2 (part 2 of the trial) was a randomised, double-blind, placebo-controlled, Phase 3 trial evaluating the combination of baricitinib + remdesivir compared to placebo + remdesivir. Patients were randomised 1:1 to baricitinib + remdesivir versus remdesivir + a matching baricitinib placebo. Patients were assessed daily while hospitalised, from Day 1 through Day 29. If the patients were discharged from the hospital prior to Day 29, study visits were planned for Days 15, 22, and 29.

Study participants

This study was conducted at a total of 67 study sites in 8 countries: United States (55 sites), Singapore (4), South Korea (2), Mexico (2), Japan (1), Spain (1), the United Kingdom (1), and Denmark (1). Patients **eligible for inclusion** were male or non-pregnant female adults ≥ 18 years of age at the time of enrolment, who:

- Were admitted to a hospital with symptoms suggestive of COVID-19.
- Had laboratory-confirmed SARS-CoV-2 infection as determined by PCR or other commercial or public health assay in any specimen, as documented by either of the following:
    - PCR positive in sample collected < 72 hours prior to randomization; OR
    - PCR positive in sample collected ≥ 72 hours prior to randomization, documented inability to obtain a repeat sample (e.g. due to lack of testing supplies, limited testing capacity, results taking > 24 hours, etc) AND progressive disease suggestive of ongoing SARS-CoV-2 infection.
- Had illness of any duration, and at least one of: Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), OR SpO2 ≤ 94% on room air, OR Requiring supplemental oxygen, OR Requiring mechanical ventilation or ECMO.

Patients meeting any of the following criteria were **excluded from participation**:

- ALT or AST > 5 times ULN; eGFR < 30 mL/min or hemodialysis/ hemofiltration; neutropenia (absolute neutrophil count <1000 cells/μL) (<1.0 x 103/μL or <1.0 GI/L); lymphopenia (absolute lymphocyte count <200 cells/μL)
- Pregnancy or breast feeding.
- Anticipated discharge from the hospital or transfer to another hospital within 72 hours.

- Allergy to any study medication.
- Receiving in the weeks prior to screening or still receiving:
    - three or more doses of remdesivir including the loading dose, outside of the study.
    - convalescent plasma or IV immunoglobulin [IVIg] for COVID-19.
    - small molecule tyrosine kinase inhibitors (e.g. baricitinib, imatibib, genfinitib).
    - monoclonal antibodies targeting cytokines (e.g., TNF inhibitors, anti-interleukin-1, anti-IL-6 [tocilizumab or sarilumab]), or T-cells (e.g., abatacept).
    - monoclonal antibodies targeting B-cell (e.g., rituximab, and including any targeting multiple cell lines including B-cells).
    - other immunosuppressants and in the judgement of the investigator, the risk of immunosuppression with baricitinib is larger than the risk of COVID-19.
    - ≥20 mg/day of prednisone or equivalent for ≥14 consecutive days.
    - probenecid.
- Diagnosis of current active tuberculosis (TB) or, latent TB treated for less than 4 weeks with appropriate anti-tuberculosis therapy per local guidelines (by history only).
- Suspected serious, active bacterial, fungal, viral, or other infection (besides COVID-19) that could constitute a risk when taking investigational product.
- Received any live vaccine (that is, live attenuated) within 4 weeks before screening, or intend to receive a live vaccine (or live attenuated) during the study.
- History of VTE (deep vein thrombosis [DVT] or pulmonary embolism [PE]) within 12 weeks prior to screening or have a history of recurrent VTE.
- Immunocompromised patients, patients with a chronic medical condition, or those taking a medication that cannot be discontinued at enrolment, who, in the judgment of PI, are at increased risk for serious infections or other safety concerns given the study products.

CHMP's assessment

The in- and exclusion criteria are considered to be appropriate and resulted in a population representative for the adult population envisioned. Most patients enrolled would be in an ordinal scale (OS)5, 6 or 7 (see for more details the table in the Comment box under 'Outcome/endpoints'). Based on the inclusion criteria, patients in OS4 - being hospitalized, not requiring supplemental oxygen but requiring ongoing medical care – will be limited. This is accepted, given that the sought indication is patients who require low-flow oxygen or non-invasive ventilation/high flow oxygen.

Treatments

Patients received baricitinib 4 mg po (two 2 mg tablets) or crushed for NG tube or placebo QD for 14 days or up to hospital discharge, whichever occurred first. All patients received a loading dose of remdesivir 200 mg IV, followed by 100 mg IV for the duration of hospitalisation up to Day 10.

VTE prophylaxis was recommended for all patients unless there was a major contraindication, such as active bleeding events or history of heparin-induced thrombosis.

CHMP's assessment

The dose of oral baricitinib 4 mg once daily and the dose of intravenous remdesivir 200 mg Day 1 followed by 100 mg up to Day 10, was conform the EU doses currently approved for both products.

The applied background regimen of remdesivir in both treatment arms hampers the evaluation of the efficacy of baricitinib monotherapy. Thereto, additional information obtained from the KHAA trial (evaluating baricitinib vs placebo in patients with COVID-19) is needed.

Objectives

The overall objective of the ACTT was to evaluate the clinical efficacy and safety of different investigational therapeutics relative to the control arm among hospitalized adults who have COVID-19.

Outcomes/endpoints

The primary outcome measure of Study ACTT-2 was the time to recovery, with the day of recovery defined as the first day, during the 28 days after enrolment, on which a patient recovered (that is, reached Category 1, 2, or 3 on the OS).

The key secondary outcome measure was to evaluate the clinical efficacy in adults hospitalized with COVID-19 according to clinical status (8-point ordinal scale) at Day 15.

Other key secondary outcome measures (multiplicity controlled) were to evaluate clinical efficacy as assessed by multiple clinical parameters:

- Proportion of patients who died or require noninvasive ventilation/high-flow oxygen or invasive mechanical ventilation (including extracorporeal membrane oxygenation [ECMO]) by Day 29
- Overall improvement on the NIAID-OS evaluated at Day 11 and Day 15
- At Least 1-Point Improvement on NIAID-OS or Live Discharge from Hospital at Day 15
- All-cause mortality (Day 1-Day 29)
- Number of ventilator-free days (Day 1-Day 29)

And to evaluate safety by cumulative incidence of SAEs through Day 29, Grade 3 and 4 AEs through Day 29 and changes in WBC with differential, haemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, AST, INR, d-dimer, CRP on Days 1, 3, 5, 8, 11, 15 and 29.

An exploratory objective was to evaluate virologic efficacy by assessment of percent of patients with detectable oropharyngeal sample, quantitative oropharyngeal sample, development of resistance at Days 3, 5, 8, 11, 15, 29 or quantitative sample in blood at Days 3, 5, 8 and 11.

CHMP's assessment

The study has been developed in the midst of a pandemic, at a time when it was not yet clear what the most appropriate endpoints would be. No scientific advice has been requested. Although time to recovery is an accepted endpoint for COVID-19 treatment studies, time to recovery may depend on different factors. For example, the difference between OS 3 and 4 seems a bit arbitrary (as OS 4 is hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (COVID-19 related or otherwise) and OS 3 is hospitalized, not requiring supplemental oxygen - no longer requiring ongoing medical care, see also the table below). Further, initial improvement may be followed by subsequent relapse. The

clinical relevance of time to recovery could be debated for these reasons, and time to sustained recovery would have been preferred.

One of the main secondary outcome measures is a one-point change in the ordinal scale at Day 15. However, one point change in ordinal scale is subject to the estimation of the individual clinician and the way oxygen systems are handled (relevant to the difference between OS 5 and 6). Further, the clinical relevance of only 1 point improvement on the ordinal scale is unknown as it can be rather subjective, and deterioration may occur after initial improvement. It is considered that a two-point change in ordinal scale is more robust, and MAH has therefore been requested to provide the proportion of patients reaching a 2-point improvement in ordinal scale by Day 15. A significantly greater proportion of patients treated with baricitinib + remdesivir compared with patients treated with placebo + remdesivir had at least a 2-point improvement on the national institute of allergy and infectious diseases (NIAID) ordinal scale (OS) at Day 15 (74.4% versus 66.2%, respectively; p=0.007).

Overall, all-cause mortality at Day 29 is considered the strongest outcome measure to play a role in the assessment.

NIAID ordinal scale categories:

Score	Descriptor
8	Death
7	Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
6	Hospitalized, on non-invasive ventilation or high flow oxygen devices
5	Hospitalized, requiring supplemental oxygen
4	Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care
3	Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care
2	Not hospitalized, limitation on activities and/or requiring home oxygen
1	Not hospitalized, no limitations on activities.

Sample size

The primary null hypothesis tested whether the time-to-recovery differs between the experimental and control arms. The log-rank test was used to compare treatment arms concerning time to recovery. For the log-rank test, the two key determinants of power were the total number of events (i.e., recoveries) E and the treatment-to-control ratio of the rate of recovery, R. The number of events required for power $1 - \beta$ to detect a recovery rate ratio of θ using a two-tailed test at alpha=0.05 is approximately

$E = 4(1.96 + z\beta\ )^2/\{\ln(\theta)\}^2$

where $z\beta$ is the $100(1 - \beta)^{th}$ percentile of the standard normal distribution. The force of recovery (sometimes loosely referred to as the "recovery ratio") is the analogue of the hazard ratio, and the term "recovery rate ratio" is the analogue of the hazard ratio in this setting. A recovery rate ratio of 1.31 was

reported for a lopinavir/ritonavir study that used the time to improve by two categories as a primary endpoint. A preliminary review of data from ACTT-1 demonstrated a recovery rate ratio of 1.312. It was unlikely the second component of treatment would have a similar effect size; therefore, a recovery ratio of 1.25 was assumed for this trial. For 85% power, 723 recoveries were required for a recovery ratio of 1.25. The study accrued until approximately 723 recoveries were achieved. The date of study closure was estimated based on enrolment rate and recovery/enrolment percentages. If approximately 70% of participants recover, the total sample size would be 1032.

An interim analysis was planned at a 33% information fraction employing a Lan-De Mets spending function with O'Brien-Flemming type of boundaries, which did not have a substantial impact on the required sample size. Conditional power was used for computation of the probability of obtaining a statistically significant result by the end of the trial given the data accumulated thus far, incorporating and assuming a hypothesized treatment effect (e.g., the treatment effect assumed for sample size determination) thereafter. If conditional power was less than 20% under the original trial assumptions, consideration was given to stopping the trial.

Interim safety data was available electronically in real-time. No formal interim safety analyses were planned.

CHMP's assessment

The assumptions concerning the anticipated treatment effect are poorly justified, though this is expected, given the lack of previous data concerning the efficacy of baricitinib in the suggested indication. The observed information (817 recoveries) was 113% of the planned (723 recoveries). The sample size calculations are endorsed.

Randomisation

Patients were randomised 1:1 to receive baricitinib + remdesivir or remdesivir + placebo and stratified by disease severity (moderate vs severe) and hospital site at enrolment. This approach minimised any risk of selection or management approach bias (including the allocation of patients to particular treatment groups based on physician judgment, which was a concern in other COVID-19 trials).

Mild to moderate disease was defined as OS 4 (not on supplemental oxygen) and OS 5 (those on low flow oxygen devices, defined as 15 L/minute or less). Severe disease was defined as participants in OS 6 (non-invasive mechanical ventilation/high-flow oxygen devices) or OS 7 (ECMO or invasive mechanical ventilation).

CHMP's comment

Randomisation by site and disease severity can be endorsed.

Blinding (masking)

As both arms are receiving remdesivir, the remdesivir product is not blinded, and study infusions can be labelled accordingly. The baricitinib/placebo component is blinded. Baricitinib and placebo tablets are identical in appearance. Unblinding of the study will occur after all subjects enrolled have reached the end of the study, and these visits are monitored, and data is cleaned, or if the DSMB recommends unblinding. In the case of (S)AEs, the individual subject can be unblinded upon request of the treating physician.

Statistical methods

Analysis populations:

- ITT Population: includes all randomised patients, classified by their randomised treatment assignment and randomised disease severity stratum. A total of 1033 patients (baricitinib + remdesivir group, 515 patients; placebo + remdesivir group, 518 patients) were included in the ITT Population. No randomised patients were excluded from the ITT Population.
- As-Treated Population (also called Safety Population): includes all randomised patients who received baricitinib/placebo study product. A total of 1016 patients (baricitinib + remdesivir group, 507 patients; placebo + remdesivir group, 509 patients) were included in the As-Treated Population; 17 patients (baricitinib + remdesivir group, 8 patients; placebo + remdesivir group, 9 patients) did not receive at least 1 tablet of baricitinib/placebo, and were excluded from the As-Treated Population.

Primary Analysis

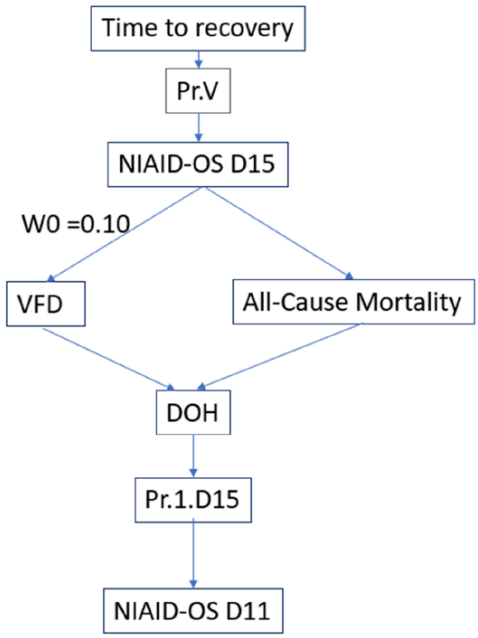
The primary efficacy endpoint was the time to recovery, where recovery was defined as having a value of 1, 2, or 3 on the clinical status 8-point ordinal scale. If a subject was discharged from the hospital prior to reporting a clinical status ordinal score (CSOS) of 1, 2, or 3, the subject was considered recovered at the time of discharge. The time to recovery was defined as the elapsed time (in days) from randomization to the earliest day at which a subject reaches recovery.

The primary analysis uses the stratified log-rank test to compare the treatment to control through Day 29 concerning time to recovery. Stratification was based on moderate versus severe disease at baseline. All deaths within 29 days would be considered censored at Day 29 with respect to time to recovery. Conceptually, a death corresponds to an infinite time to recovery, but censoring at any time greater than or equal to Day 29 gives the same answer as censoring at Day 29; both correspond to giving deaths the worst rank. If the assumption of proportional hazards is not justified, a statistical model capable of handling nonproportional hazards is explored to assess treatment effect, such as a max- Combo test, restricted mean survival time model, and win ratio analysis.

Multiple Comparisons/Multiplicity

Multiplicity-controlled analyses will be performed on the primary and key secondary endpoints to control the overall family-wise Type I error rate at a 2-sided α level of 0.05. The graphical multiple testing procedure is displayed in Figure 3 below.

Figure 3 Graphical testing scheme for ACTT-2



Abbreviations: D = Day; DOH = duration of hospitalization; NIAID OS = National Institute of Allergy and Infectious Disease ordinal scale; Pr.1D15 = proportion of patients with at least 1-point improvement on the NIAID-OS or live discharge from the hospital at Day 15; Pr.V = proportion of patients who died or required noninvasive ventilation/high-flow oxygen or invasive mechanical ventilation (including extracorporeal membrane oxygenation [ECMO]) by Day 29; VFD = ventilator-free days; W = Weight.

Handling of Dropouts or Missing Data

Several methods for treating dropouts and/or missing data are reported in the SAP, the CSR ad the respective Addendums. The most relevant are cited here.

Infinite Event Time Imputation (IETI)

For some time-to-event endpoints, if there are competing risks to the event of interest, then the event times censored due to the competing risk will be imputed as infinite. This imputation method will be applied if the event of interest is in the opposite direction of death (e.g., recovery or improvement). For time to recovery or time to improvement, all deaths within 29 days will be considered censored at Day 29 with respect to time to event of interest. Conceptually, a death corresponds to an infinite time to an event of interest, but censoring at any time greater than or equal to Day 29 gives the same answer as censoring at Day 29; both correspond to giving death the worst rank.

Modified Last Observation Carried Forward (mLOCF)

A modified last observation carried forward (mLOCF) analysis is performed by carrying forward the last postbaseline assessment for the continuous measures or ordinal scale measures, assuming that effects of treatments remain the same after the occurrence of the intercurrent event. After mLOCF imputation, data from patients with nonmissing baseline and at least 1 postbaseline observation will be included in the analyses. These mLOCF analyses help ensure that the maximum number of randomized patients who were assessed postbaseline will be included in the analyses. For patients who experience any intercurrent event at any time, the last nonmissing postbaseline observation on or prior to this event will be carried forward to subsequent time points for evaluation. If a patient does not have a nonmissing observed record (or one imputed by other means) for a postbaseline visit prior to discontinuation or rescue, the last postbaseline record prior to the missed visit will be used for the visit. This imputation method is consistent with while-on-treatment strategy. Details for the mLOCF strategy can be found in the CSR.

CHMP's comment

In addition to the above remarks concerning "sustained recovery", the proportion of imputed NIAID-OS scores is of direct relevance. Specifically, what is the proportion of patients for whom recovery was assessed on the basis of a measurement prior to day 29 and subsequently their scores had to be imputed (and according to the imputation rules, recovery would be sustained by the mLOCF strategy)**.** The MAH has explained that no imputation has been applied and that any patients who were lost to follow-up or who terminated early were censored at the day of their last observed assessment. Patients who completed follow-up but did not experience recovery were censored at the day of their Day 29 visit. This is acceptable. However, the proportion of patients for which recovery was observed (and thus counted as an event) and were subsequently lost to follow-up remains unclear. Since the number of patients with unknown status by Day 29 after initial recovery is similar for both groups and as the proportion of patients with sustained recovery is comparable for both groups, no major differences in the outcome between placebo and baricitinib arms are anticipated here and this is not further pursued.

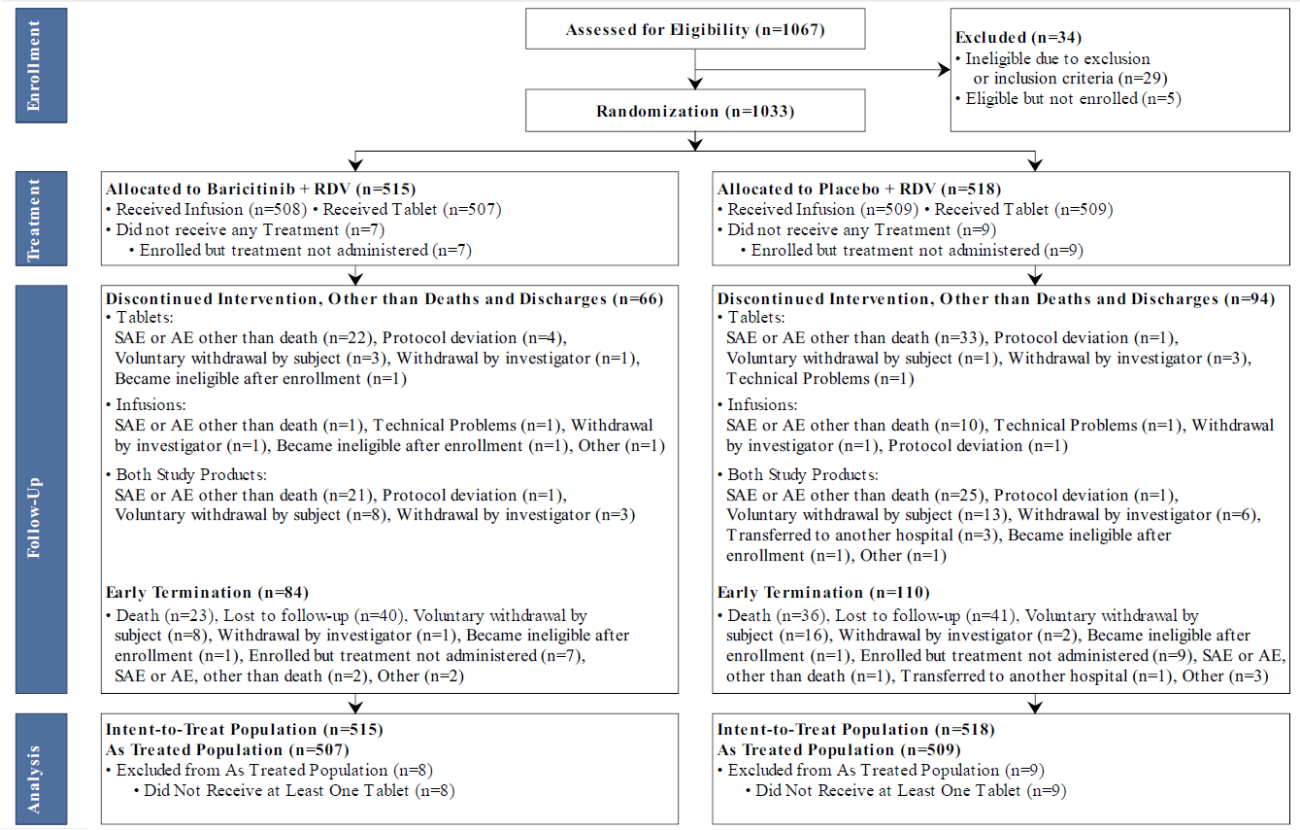
Furthermore, it is agreed that the strategy for handling intercurrent events is consistent with the while-on- treatment strategy. Upon request, the MAH clarified that the use of concomitant medications was ignored in the main analysis (that is, data for patients who used concomitant medications were not censored) and that no intercurrent event has been considered in the main analysis. This is acceptable. It has also been clarified that administration of concomitant medication was not considered an intercurrent event for all time-to-event analyses, which is endorsed. In the mortality analysis, the endpoint was assessed as time to death without consideration of any intercurrent events. This is acceptable. Finally, the main analysis for all time-to-event outcomes considered concomitant medication (including corticosteroid use) as part of standard of care (SOC), which is acceptable.

Results

Participant flow

The Participant flow is illustrated in the flow chart in Figure 4. A total of 1067 subjects were screened, of whom 1033 were randomized and included in the ITT population. A total of 34 subjects were either ineligible or were eligible but did not enrol and an additional 16 randomized subjects did not receive study treatment. The most common reason for screening failure was that the subject anticipated discharge from the hospital or transfer to another hospital which was not a study site within 72 hours.

Figure 4 Subject disposition ACTT-2



Recruitment

Date of first enrolment: 08 May 2020. Date of last visit: 31 July 2020. Subjects were enrolled and treated at 78 clinical study sites globally (US, Spain, Mexico, Japan, Singapore, Rep of Korea, Denmark, UK).

CHMP's comment

The study was conducted at a total of 67 study sites in 8 countries: United States (55 sites), Singapore (4), South Korea (2), Mexico (2), Japan (1), Spain (1), the United Kingdom (1), and Denmark (1).

Conduct of the study

Analysis populations

A total of 1033 subjects (Baricitinib + RDV group, 515 subjects; Placebo + RDV group, 518 subjects) were included in the ITT population. No subjects were excluded from the ITT population. For the SAP based ITT analyses, subjects were classified by their randomized treatment assignment and randomized disease severity stratum.

However, a larger than anticipated number of stratification errors (forty-four) for disease severity occurred at the time of randomization. Forty-two errors were for subjects who were moderately-severe but incorrectly entered as a severe disease at the time of randomization. Conversely, two cases were subjects with severe disease incorrectly entered as a moderate disease at the time of randomization. This results in a 40 subject net difference in the moderate and severe categories in the Randomized Disease Severity and Actual Disease Severity populations.

A single site was responsible for 32 errors. After investigation at that site, it was determined that the investigator conducting the randomization incorrectly translated the non-invasive ventilation ordinal score from English to Spanish and subsequently miscategorized subjects on low-flow nasal cannulas as "noninvasive ventilation" instead of "requires supplemental oxygen." At the other sites, six stratification errors were reported as being due to data entry error, and the other six were due to misinterpretation of the oxygen device categorization and mis-categorization of disease severity at the time of randomization.

Given that the sites knew the severity of illness and treated accordingly, the actual strata should be used for clinical guidance and a measure of the true effectiveness of the primary result. Therefore additional ad hoc tables and figures are presented for the efficacy outcomes using the ITT and As Treated populations with subjects classified by their actual disease severity stratum.

CHMP's comment

Considering the number of stratification errors for disease severity, the main analysis population for evaluating efficacy will be the **treated population** (subjects who received at least a dose of study treatment) **randomised by actual disease severity**.

As 44 stratification errors occurred for disease severity (misclassification between OS 5 and 6) and since most stratification errors occurred at one study site (32 of 44), the MAH has been requested to provide analyses of the primary and secondary outcome measures (time to recovery, all-cause mortality, progression to death or ventilation and overall improvement on the ordinal scale at Day 15) by ordinal scale leaving out the results of the study centre with stratification errors. Results of the analyses are consistent with the results for the full As-Treated population.

Protocol amendments

Based on the original protocol, there have been several amendments laid down in different versions of the protocol:

- Version 2.0, 2 March 2020: main changes relating to an increased number of study sites, sample size increased, ordinal scale increased to 8 categories, inclusion criteria, separation of objectives for non-invasive and invasive mechanical ventilation, added Day 14 mortality, viral load in plasma and resistance
- Version 3.0, 27 March 2020: main changes relating to sample size increased, change of the primary endpoint from an ordinal scale on a given day to days to recovery (categories 1-3 of the ordinal scale), in- and exclusion criteria, increased number of study sites, concomitant therapy
- Version 4.0, 13 April 2020: main changes relating to the addition of the additional treatment stage "ACTT-2" and separation of the general study protocol from specific appendices A (ACTT-1) and B (ACTT-2), subsequent modifications to create appendix B dedicated to the addition of baricitinib or placebo to remdesivir treatment, with the adoption of the objectives and in-/exclusion criteria of ACTT-1
- Version 5.0, 4 May 2020: main changes relating to the calculation of a new sample size to reflect the 2 arm design and the likely lower anticipated treatment effect of a second agent, potential risks of baricitinib, stratification was revised to match ordinal scale categories, exploratory endpoints for cytokine assessments
- Version 6.0, 21 May 2020: main changes relating to the use of prior and concomitant medication

CHMP's assessment

Different protocol amendment histories have been described in different documents included in the CTD. Whereas the protocol amendment history provided above (as displayed in Protocol Number: 20-0006, page 46) lists 6 versions of the protocol, only three versions have been listed in Section 16.1/Study Information. As all required information can be obtained from the CTD, this issue is not further pursued.

With the last amendment (version 6.0, 21 May 2020) the permitted length or amount of prior or concomitant medication was adjusted. This amendment was dated after the first enrolment in the study (8 May 2020), but prior to the last enrolment (31 July 2020) and database lock (10 September 2020). No differences between the study arms as a result of this amendment is anticipated.

Protocol deviations

There were 308 major subject-specific protocol deviations. The most common category of major protocol deviation was protocol procedure or assessment deviations (64 deviations), with 18 deviations for prohibited medications and 14 deviations for a required procedure that was done incorrectly. Treatment administration deviations were the second most common category of major protocol deviations (55 deviations), with 17 deviations for a required procedure done incorrectly and 5 deviations for missed treatment administration.

Fifty-eight non-subject specific protocol deviations were reported, with the most common categories of major protocol deviations being protocol procedure or assessment (n=17) and treatment administration (n=7)

Baseline data

Demographic and baseline characteristics are presented in Table 10. Demographics and baseline characteristics were similar between the Baricitinib + RDV and Placebo + RDV groups. Most subjects in the ITT population were male (63%) between 40 – 64 years (54%) with a mean age of 55.4 years (range: 18 to 101 years); most were white (48%) or unknown (25%). The mean (SD) BMI was 32.21 (8.29) kg/m2. Most subjects (64%, 666 subjects) were in the moderate disease stratum. The median duration of symptoms prior to enrolment was 8.0 days for both treatment groups. Most subjects had 1 (25%) or 2 or more (56%) comorbidities at enrolment. The most commonly reported comorbidities were obesity (56%), hypertension (52%), and type 2 diabetes mellitus (37%). Baseline clinical status was similar between the two treatment groups. A total of 111 subjects (11%) had a clinical status of 7 (hospitalized, receiving invasive mechanical ventilation or ECMO), 216 subjects (21%) had a clinical status of 6 (hospitalized, receiving non-invasive ventilation or high flow oxygen devices), 564 subjects (55%) had a clinical status of 5 (hospitalized, requiring supplemental oxygen), and 142 subjects (14%) had a clinical status of 4 (hospitalized, not requiring supplemental oxygen, requiring ongoing medical care [COVID-19-related or otherwise]).

Table 10 Demographic and baseline characteristics ACTT-2, ITT population

Demographic Characteristic		**Baricitinib + remdesivir (N=515)** n (%)	**Placebo + remdesivir (N=518)** n (%)	**All subjects (N=1033)** n (%)
Sex	Male	319 (62)	333 (64)	625 (63)
	Female	196 (38)	185 (36)	381 (37)
Race	American Indian, Alaska Native	2 (<1)	8 (2)	10 (1)
	Asian	49 (10)	52 (10)	101 (10)
	Native Hawaiian or other Pacific Islander	4 (1)	7 (1)	11 (1)
	Black or African American	77 (15)	79 (15)	156 (15)
	White	251 (49)	245 (47)	496 (48)
	Unknown	132 (26)	127 (25)	259 (25)
Age	< 40 years	87 (17)	86 (17)	173 (17)
	40-64 years	281 (55)	274 (53)	555 (54)
	≥ 65 years	147 (29)	158 (31)	305 (30)
Baseline OS	4	70 (14)	72 (14)	142 (14)
	5	288 (56)	276 (53)	564 (55)
	6	103 (20)	113 (22)	216 (21)
	7	54 (10)	57 (11)	111 (11)
Comorbidities	No comorbidities	64 (12)	91 (18)	155 (15)
	1 comorbidity	148 (29)	122 (24)	270 (26)
	2 or more comorbidities	284 (55)	285 (55)	569 (55)
	Unknown	19 (4)	20 (4)	39 (4)
Demographic Characteristic, Mean (SD)				
Age		55 (15.4)	55.8 (16)	55.4 (15.7)
Weight (kg)		90.8 (24.8)	91 (25.1)	90.9 (24.9)
BMI (kg/m^2)		32.16 (8.17)	32.25 (8.41)	32.21 (8.29)
Duration of symptoms prior to enrolment		8.3 (4.4)	8.6 (4.6)	8.5 (4.5)

CHMP's assessment

Baseline characteristics were well balanced between the two arms of the study.

Concomitant medications

Corticosteroids were the most common medication of interest used (22%, n=223 subjects). Subjects in the moderate stratum reported comparable use of corticosteroids for both treatment groups (18% for baricitinib vs. 15% for placebo); subjects in the severe stratum reported 39% use of corticosteroids in the Placebo + RDV group compared to 28% in the Baricitinib + RDV group.

CHMP's assessment

In the severe disease stratum, the proportion of patients using corticosteroids was higher in the placebo group vs the baricitinib group (39% vs 28%). For more details regarding concomitant corticosteroid therapy, see the Ancillary Analysis section.

Treatment compliance

33% of subjects received all 10 infusions of Remdesivir (Baricitinib + RDV group, 175 subjects; Placebo + RDV group, 169 subjects) and 15% of subjects received all 14 doses of Baricitinib/Placebo (Baricitinib + RDV group, 76 subjects; Placebo + RDV group, 81 subjects). 66% of subjects in the Baricitinib + RDV group received less than 14 doses due to discharge compared to 59% of subjects in the Placebo + RDV group. 9 subjects received less than 14 doses of Baricitinib/Placebo due to death (Baricitinib + RDV group, 2 subjects; Placebo + RDV group, 7 subjects) and 6 subjects received less than 10 infusions of Remdesivir due to death (Baricitinib + RDV group, 1 subject; Placebo + RDV group, 5 subjects).

Numbers analysed

A total of 1033 subjects (Baricitinib + RDV group, 515 subjects; Placebo + RDV group, 518 subjects) were included in the ITT population. No subjects were excluded from the ITT population. The As Treated population included all randomized subjects who received the barcitinib/placebo study product, even if only one tablet was administered. A total of 1016 subjects (Baricitinib + RDV group, 507 subjects; Placebo + RDV group, 509 subjects) were included in the As Treated population. 17 subjects (Baricitinib + RDV group, 8 subjects; Placebo + RDV group, 9 subjects) did not receive at least one tablet of Baricitinib/Placebo and were excluded from the As Treated population. Table 11 illustrates the numbers of subjects by analysis population and disease severity stratum, by randomized disease severity. Table 12 illustrates the numbers of subjects by analysis population and disease severity stratum, by actual disease severity.

Table 11 Numbers of subjects by treatment group and randomized disease severity

		Baricitinib + RDV		Placebo + RDV		All Subjects	
		Moderate	Severe	Moderate	Severe	Moderate	Severe
Analysis Population	**Inclusion/Reason for Exclusion**	**n**	**n**	**n**	**n**	**n**	**n**
Intention-to-Treat Population	Included in Population[a]	339	176	327	191	666	367
As Treated Population	Included in Population[b]	333	174	322	187	655	361
	Excluded from Population[a]	6	2	5	4	11	6
	Did Not Receive at least one tablet[a]	6	2	5	4	11	6

[a] Counts are the numbers of subjects randomized to the specified treatment group and randomized disease severity stratum.
[b] Counts are the numbers of subjects in the randomized disease severity stratum who received the specified treatment.

Table 12 Numbers of subjects by treatment group and actual disease severity

		Baricitinib + RDV		Placebo + RDV		All Subjects	
		Moderate	Severe	Moderate	Severe	Moderate	Severe
Analysis Population	**Inclusion/Reason for Exclusion**	**n**	**n**	**n**	**n**	**n**	**n**
Intention-to-Treat Population	Included in Population[a]	358	157	348	170	706	327
As Treated Population	Included in Population[b]	352	155	343	166	695	321
	Excluded from Population[a]	6	2	5	4	11	6
	Did Not Receive at least one tablet[a]	6	2	5	4	11	6

[a] Counts are the number of subjects in the actual disease severity stratum and randomized to the specified treatment group.
[b] Counts are the numbers of subjects in the actual disease severity stratum who received the specified treatment.

CHMP comment

As commented above, the relevant population for evaluation of efficacy by disease severity is the as treated population randomized by actual disease severity.

In ACTT-2, the ITT and As Treated populations differ by n=17, with 515 (baricitinib+RDV) and 518 (PBO+RDV) patients in the ITT group and 507 (baricitinib+RDV) and 509 (PBO+RDV) patients in the As Treated group. Nevertheless, in Table 7 and Table 8, the number of patients for which the TTR endpoint is reported is exactly the same for ITT and As Treated populations, while, based on the above, it is expected that the ITT population might or could contain up to 17 patients more than the As Treated population in the analysis of the primary endpoint. Upon request the MAH explained that the 'n' column in these 2 tables is the number of recovered patients, not the number of patients for whom the time to recovery endpoint is reported. No patients who were in the intent-to-treat (ITT) population, but not in the As-Treated population, recovered. Since all patients who reached recovery status were patients who were treated (dosed) during the study, the number of recovered patients is the same in the ITT Population and the As-Treated Population.

Outcomes and estimation

Primary efficacy endpoint

In the ITT population the Baricitinib + RDV group had a 15% higher hazard of recovery than the Placebo + RDV group (RR 1.15; 95% CI: 1.00, 1.31; p=0.047) with a median recovery time of 7 days (95% CI: 6.0, 8.0) compared to 8 days (95% CI: 7.0, 9.0) in the Placebo + RDV arm.

In the As treated population (actual disease severity) the rate ratio (RR) for recovery was 1.16 in favour of the Baricitinib + RDV group (95% CI: 1.01, 1.33; p=0.032) with a median recovery time of 7 days (95% CI: 6.0, 8.0) compared to 8 days (95% CI: 7.0, 9.0) in the Placebo + RDV arm.

Figure 5 shows the Kaplan Meier curve for time to recovery. A summary of recoveries and deaths by Day 29 is provided in Table 13.

Figure 5 Kaplan Meier curve of Time to Recovery

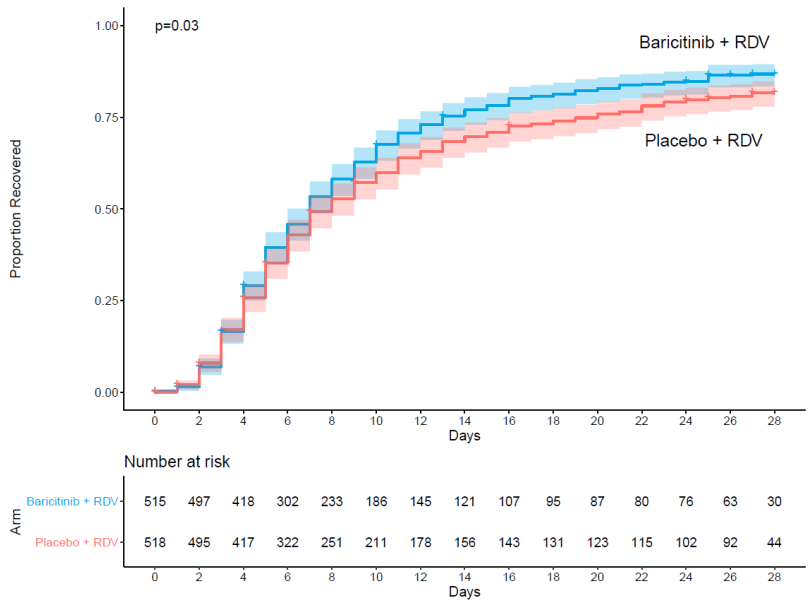


Table 13 Summary of recoveries and deaths by Day 29, by randomized disease severity and pooled duration of symptoms (ITT population)

			Recovered		Did Not Recover		Deaths		Not Recovered or Died	
Grouping Variable	**Subgroup**	**Treatment Group**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Randomized Disease Severity	Moderate	Baricitinib + RDV (N=339)	311	92	24	7	5	1	29	9
		Placebo + RDV (N=327)	292	89	24	7	12	4	36	11
	Severe	Baricitinib + RDV (N=176)	122	69	35	20	19	11	54	31
		Placebo + RDV (N=191)	114	60	52	27	25	13	77	40
	Any Severity	Baricitinib + RDV (N=515)	433	84	59	11	24	5	83	16
		Placebo + RDV (N=518)	406	78	76	15	37	7	113	22
Pooled Duration of Symptoms Group 1	First Quartile (<= 5 Days)	Baricitinib + RDV (N=134)	115	86	14	10	6	4	20	15
		Placebo + RDV (N=130)	101	78	20	15	9	7	29	22
	Second Quartile (6 to <= 8 Days)	Baricitinib + RDV (N=159)	130	82	18	11	11	7	29	18
		Placebo + RDV (N=161)	129	80	21	13	12	7	33	20
	Third Quartile (9 to <= 10 Days)	Baricitinib + RDV (N=96)	81	84	11	11	4	4	15	16
		Placebo + RDV (N=84)	71	85	8	10	5	6	13	15
	Fourth Quartile (11+ Days)	Baricitinib + RDV (N=120)	107	89	10	8	3	3	13	11
		Placebo + RDV (N=133)	105	79	17	13	11	8	28	21

CHMP's assessment

Although the significant difference in time to recovery in favour of the Baricitinib + RDV group is acknowledged, the clinical relevance of the one day difference is limited.

Further, the primary endpoint of time to recovery was based on a patient's initial recovery. Thus subjects could have initial improvement with subsequent deterioration. The MAH is requested to clarify if an ordinal scale assessment has been performed after initial recovery and if so, to provide a summary of these data and to analyse the time to sustained recovery. Specifically, Table 14 of the main CSR indicates that for approximately 19% of the patients (195/1033), an OS measurement was not available at Day 29, and thus recovery (and even sustained recovery) can only be based on the mLOCF imputation rules**.** The MAH explained that one patient in each treatment group died following recovery. There were no clinically meaningful differences in progression between the treatment groups. Time to recovery after censoring readmittance of recovered cases at Day 28 showed a numerical benefit for the baricitinib + remdesivir group over the placebo + remdesivir group, but the effect of baricitinib on sustained recovery is not statistically significant (95% CI includes 1). Furthermore, the proportion of recovered patients that reached a sustained recovery status was marginally larger in the placebo group. Proportion of (sustained) recovered patients is not significantly different between the two groups (analysis conducted by CHMP). These observations illustrate that the observed effect in the primary outcome was already limited as the small number of patients censored for the sensitivity analysis, results in the difference between the groups being no longer significant.

The KM curves illustrate that curves start to separate from Day 8 and stay more or less parallel from Day 8 onwards.

From Table 13 it is appreciated that 84% of patients in the Baricitinib + RDV group recovered vs 78% of patients in the Placebo + RDV group. 5% of patients treated with Baricitinib + RDV died vs 7% of patients treated with Placebo + RDV. This indicates an overall beneficial effect of baricitinib treatment. However, the proportion of patients who did not recover and did not die by Day 29 was 16% in the Baricitinib + RDV group vs 22% in the Placebo + RDV group. This is a significant proportion of patients who do not have a clear outcome at D29, which impact the overall conclusions that can be drawn based upon the data provided. Upon request, the MAH has explained that for ACTT-2, no data are available after Day 29 and thus uncertainty remains regarding the large proportion of patients for whom clinical status is not known (ie patients who did not recover and did not die by Day 29).

Secondary efficacy endpoints

Progression to death or progression to noninvasive ventilation/high-flow oxygen or invasive mechanical ventilation (including ECMO): A significantly smaller proportion of patients treated with baricitinib + remdesivir compared to patients treated with placebo + remdesivir died or progressed to ventilation (23% vs 29%; OR 0.73; p = 0.03), as is illustrated in Table 14.

Table 14 Proportion of Patients Who Died or Required Noninvasive Ventilation/High-Flow Oxygen or Invasive Mechanical Ventilation, As-Treated Population

Baseline OS		PBO+RDV (N=509)	BARI 4-mg+RDV (N=507)
Overall	n	509	507
Actual disease severity	responder (%) (a)	147 (28.9)	115 (22.7)
	95% CI (b)	(25.1, 33.0)	(19.3, 26.5)
	95% CI Diff (b)		-6.2 (-11.5, -0.8)
	95% CI Odds Ratio (e)		0.73 (0.55, 0.97)
	P-value vs. PBO+RDV (e)		0.028

Abbreviations: CI = confidence interval; N = number of patients in the analysis population; n = number of patients in the specified category.
ACTT-2: Adaptive COVID-19 treatment trial-2.
NIAID OS: National institute of allergy and infectious diseases ordinal scale for clinical status.

Overall improvement on the NIAID-OS evaluated at Day 11 and Day at Days 15: The odds of clinical improvement at Day 15 were significantly greater in patients treated with baricitinib + remdesivir compared to patients treated with placebo + remdesivir (OR 1.26, 95%CI 1.01-1.58; p=0.041, see Table 15). Similar results were observed for Day 11. Treatment group differences were statistically significant (p <.05) from Day 8 through Day 29.

Table 15 Ordinal scale distribution at Day 15, As Treated population

NIAID OS	PBO+RDV (N=509) n (%)	BARI 4-mg+RDV (N=507) n (%)	Total (N=1016) n (%)	OR 95% CI	P-Value(a)
Day 15					
1	165 (32.4)	177 (34.9)	342 (33.7)	1.26 (1.01, 1.58)	0.041
2	163 (32.0)	177 (34.9)	340 (33.5)		
3	3 (0.6)	8 (1.6)	11 (1.1)		
4	16 (3.1)	30 (5.9)	46 (4.5)		
5	47 (9.2)	38 (7.5)	85 (8.4)		
6	17 (3.3)	20 (3.9)	37 (3.6)		
7	81 (15.9)	47 (9.3)	128 (12.6)		
8	17 (3.3)	10 (2.0)	27 (2.7)		

Abbreviations: N = number of patients in the analysis population.
ACTT-2: Adaptive COVID-19 treatment trial-2.
NIAID OS: National institute of allergy and infectious diseases ordinal scale for clinical status.
(a) Odds ratio and p-values are calculated using proportional odds model analysis with treatment, randomized disease severity at baseline as covariate.
(b) Odds ratio and p-values are calculated using proportional odds model analysis with treatment, actual disease severity at baseline as covariate.
The data supports this table was transferred on 2020-12-10.

At Least 1-Point Improvement on NIAID-OS or Live Discharge from Hospital at Day 15: A greater proportion of patients treated with baricitinib + remdesivir compared to patients treated with placebo + remdesivir had at least 1-point improvement on the NIAID-OS at Day 15 (81.9% vs 72.3%, OR 1.78 (1.30, 2.44). These data did not achieve multiplicity-controlled statistical significance.

All-cause mortality by Day 29: In the as-treated population (by randomized disease severity), there was a numerical reduction in mortality; however, this was not statistically significant (the trial was not powered to demonstrate an effect on mortality). In the baricitinib + remdesivir group 23/507 died and in the placebo + remdesivir group 37/509 patients died, resulting in mortality rates of 4.5% versus 7.3% (HR = 0.63 [95% CI: 0.37, 1.05]; p=.075).

Number of ventilator-free days (Day 1-Day 29):

Mean and median ventilator-free days were 20.4 vs 22.1 and 28.0 vs 28.0 for the baricitinib + RDV and placebo + RDV groups, respectively. Patients treated with baricitinib + RDV had a higher least-squares mean number of ventilator-free days (days that patients do not have a NIAID-OS of 6 or 7) than patients treated with placebo + RDV (18.8 days versus 20.2). These data did not achieve multiplicity-controlled statistical significance.

CHMP's assessment

In the as-treated population, a significantly smaller proportion of patients in the baricitinib group died or progressed to non-invasive ventilation/high-flow oxygen, or invasive mechanical ventilation (including ECMO) compared to the placebo group (23% vs 29%; OR 0.73; p = 0.03). The odds of clinical improvement at Day 15 were significantly greater in patients treated with baricitinib + remdesivir compared to patients treated with placebo + remdesivir (OR 1.26, 95%CI 1.01-1.58; p=0.041). *A greater proportion of patients treated with baricitinib + remdesivir compared to patients treated with placebo + remdesivir had at least 1-point improvement on the NIAID-OS at Day 15, although a one-point improvement on the ordinal scale is considered to be of limited relevance and the result did not achieve multiplicity-controlled statistical significance. There was a numerical reduction in mortality that also did not reach statistical significance, with mortality rates of 4.5% and 7.3% for the baricitinib and placebo groups respectively (HR = 0.63 [95% CI: 0.37, 1.05]; p=.075). Patients treated with baricitinib + RDV had a higher least-squares mean number of ventilator-free days (days that patients do not have an NIAID-OS of 6 or 7) than patients treated with placebo + RDV (18.8 days versus 20.2). Also, these data did not achieve multiplicity-controlled statistical significance.*

Furthermore, all-cause mortality has been analysed as a time-to-event outcome with a 29-days follow-up, providing an estimate of the hazard ratio (HR). However, the comparison of mortality rates until day 29 is considered a clinically relevant effect size, and thus the MAH has been requested to provide a logistic-regression based analysis, alongside the associated risk and odds ratios of mortality within 29 days. Results of logistic regression analyses for mortality by Day 29 have been provided and are consistent with results of the log-rank analyses. Notably, the evidence for overall mortality within 29 days is slightly weaker as compared to the time-to-event analysis (p-values slightly larger).

Taken together the results for the secondary outcome measures in the overall population do show a trend towards benefit from baricitinib treatment, but did not achieve statistical significance.

Ancillary analyses

Sensitivity analyses of the primary outcome measure

In general, results for all prespecified **sensitivity analyses of the primary outcome** were consistent with those for the primary analysis:

- An analysis using Cox proportional hazards model to estimate the HR, in which subjects who die prior to recovering were treated as experiencing a competing risk in the Fine-Gray proportional hazards regression model, showed an HR consistent with the primary efficacy analysis.
- A covariate-adjusted Cox proportional hazards model of time to recovery controlling for age, duration of symptoms prior to enrolment, baseline d-dimer, and baseline CRP values as continuous covariates showed an estimated HR of 1.18 (95% CI: 1.02, 1.36), consistent to that of the primary analysis.
- Further sensitivity analyses were conducted using Cox proportional hazards models, including binary indicators for treatment group and disease severity stratum (randomized or actual severity were analysed in separate models), as well as a treatment*severity interaction term. Results in each

model were consistent with the randomized severity strata results in the primary analysis with no interaction term. The interaction term was not statistically significant.

Additional supportive analyses were conducted **stratifying by baseline ordinal score** rather than severity stratum. A Fine-Gray proportional hazards regression model was conducted for each baseline ordinal score. The Baricitinib + RDV group had a 51% higher hazard of recovery than the Placebo + RDV group (HR 1.52; 95% CI: 1.11, 2.06) in subjects with a baseline score of 6, that decreased to a 17% higher hazard of recovery (HR 1.17; 95% CI: 1.00, 1.37) in subjects with a baseline score of 5. Confidence intervals for the hazard ratio in groups 4 and 7 included 1.00. Median time to recovery by baseline ordinal scale is depicted in Table 16.

Table 16 Summary of Study ACTT-2 results by treatment group by Ordinal Score at baseline As-Treated population

	Overall		Baseline OS 4 (No supplemental oxygen)		Baseline OS 5 (Low-flow oxygen)		Baseline OS 6 (Noninvasive ventilation or high-flow oxygen)		Baseline OS 7 (Mechanical ventilation/ECMO)	
	PBO + RDV	BARI + RDV	PBO + RDV	BARI + RDV	PBO + RDV	BARI + RDV	PBO + RDV	BARI + RDV	PBO + RDV	BARI + RDV
Time to recovery										
N	509	507	70	69	273	283	111	103	55	52
Median, days (95% CI)	8.0 (7.0, 9.0)	7.0 (6.0, 8.0)	4.0 (4.0, 6.0)	5.0 (4.0, 6.0)	6.0 (5.0, 6.0)	5.0 (5.0, 6.0)	8.0 (3.0, 21.0)	0.0 (0.0, 13.0)	NR (26.0, NR)	NR (25.0, NR)
Rate Ratio[a] (95% CI) p-value[b]	1.15 (1.00, 1.32) p=.043		0.88 (0.62, 1.23) p=.441		1.17 (0.98, 1.39) p=.079		1.51 (1.10, 2.08) p=.010		1.11 (0.61, 2.02) p=.736	

Abbreviations: n = number of patients in specified category; N = number of patients in the specified treatment group, disease severity, and analysis population; NR = not reached; OR = odds ratio; OS = ordinal scale.

a Rate ratio is the HR of the time to recovery in each treatment group estimated from the Cox model. The ratio is BARI + RDV to PBO + RDV. The ratio for the "Overall" group is the ratio from the stratified Cox model.

b p-value was calculated using the stratified log-rank test.

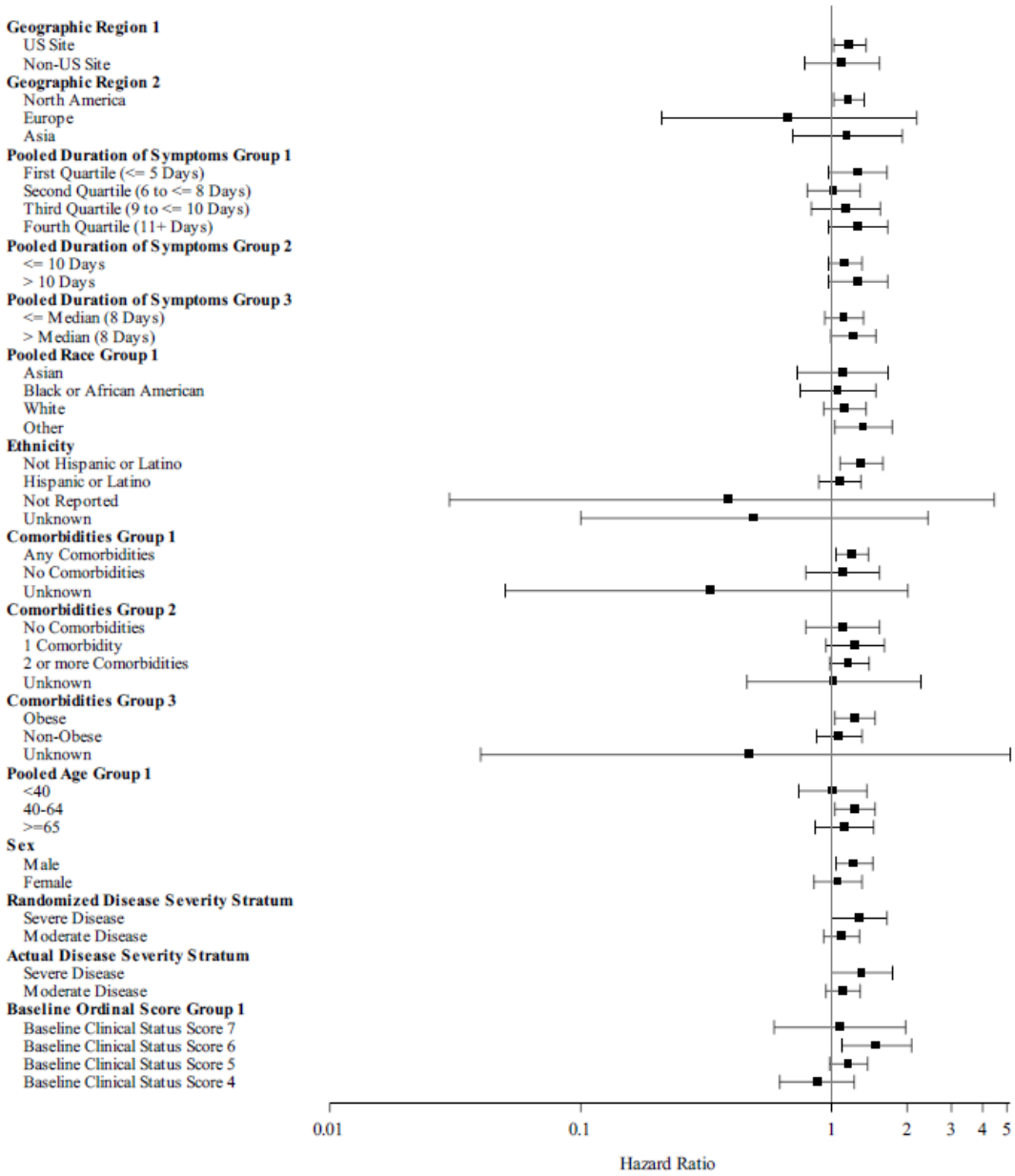
CHMP's assessment

As can be appreciated from the table displaying time to recovery by baseline ordinal scale, the primary efficacy results for the overall population are mainly driven by the beneficial effect observed in baseline ordinal scale 6 and ordinal scale 5 to a lesser extent. While in baseline ordinal scale 4 a trend towards an opposite effect can be observed, and in baseline ordinal scale 7, too few patients recovered to determine the primary outcome measure. This may indicate that treatment with baricitinib could be most beneficial if administered within a certain stage/severity of coronavirus disease (as has also been suggested for dexamethasone and remdesivir treatment), and which in the case of baricitinib may be limited to those patients with baseline ordinal scales 5 and 6, i.e. patients who are requiring supplemental oxygen (OS5) or are on non-invasive ventilation or high flow oxygen devices (OS6). This observation has adequately been reflected in the proposed indication for treatment of hospitalised COVID-19 patients who require low-flow oxygen or noninvasive ventilation/high-flow oxygen.

Subgroup analysis for the primary outcome measure

The primary analysis was repeated for different **subgroups (geographic region, duration of symptoms, race, comorbidities, age, sex, severity of disease)**. Each subgroup was considered separately. Generally, results were consistent with the primary analysis showing HRs in favour of the Baricitinib + RDV arm. In the Geographic Region 2 subgroup, Europe exhibited an HR of 0.67 (95% CI: 0.21, 2.18) favouring the Placebo + RDV arm, possibly explained by only 13 subjects providing data towards this estimate as reflected in the wider confidence interval. A forest plot of hazard ratios by subgroup is presented in Figure 6.

Figure 6 Forest plot of Hazard Ratios of Time to Recovery by subgroup (ITT)



CHMP'S assessment

Results of the primary efficacy analyses were generally consistent across subgroups.

Subgroup analyses of secondary outcome measures

Results of the subgroup analysis for secondary outcome measures are illustrated in Table 17. For the analysis of patients who died or required noninvasive ventilation/high-flow oxygen or invasive mechanical ventilation (including ECMO), the clinical benefit of baricitinib was most apparent in patients requiring supplemental oxygen at baseline (OS 5 and 6).

With regard to Day 29 mortality, the baricitinib treatment effect was most apparent in patients who were in OS 5 and 6 at baseline, where 60% and 42% relative reductions were observed in patients receiving baricitinib + remdesivir compared to patients receiving placebo + remdesivir, respectively. A reduction in mortality was not observed in the relatively small subgroup of patients with OS 7 at baseline.

In the number of ventilator-free days and invasive-ventilator-free days, the baricitinib treatment effect was most pronounced in patients who were OS 6 or 7 at baseline, with 3.2 and 2.7 fewer days of ventilation required, respectively.

For the proportion of patients achieving at least 1-point improvement on the NIAID OS at Day 15, the benefit was most pronounced in patients who were OS 5, 6, or 7 at baseline, while in patients with baseline OS 4, the OR for improvement was in favour of placebo (data not shown here, please refer to page 55 CSR addendum).

Table 17 Summary of Study ACTT-2 secondary efficacy results by treatment group by Ordinal Score at baseline As-Treated population

	Overall		Baseline OS 4 (No supplemental oxygen)		Baseline OS 5 (Low-flow oxygen)		Baseline OS 6 (Noninvasive ventilation or high-flow oxygen)		Baseline OS 7 (Mechanical ventilation/ECMO)	
	PBO + RDV	BARI + RDV	PBO + RDV	BARI + RDV	PBO + RDV	BARI + RDV	PBO + RDV	BARI + RDV	PBO + RDV	BARI + RDV
Proportion of patients progressing to ventilation or death through Day 29[c]										
N	509	507	70	69	273	283	111	103	55	52
Estimate % (95% CI)	29 (25, 33)	23 (19, 27)	3 (1, 10)	1 (0, 8)	32 (26, 37)	25 (20, 30)	42 (34, 52)	31 (23, 41)	22 (13, 34)	21 (12, 34)
OR (95% CI) p-value[d]	0.73 (0.55, 0.97) p=.030		0.60 (0.08, 4.74) p=.628		0.73 (0.50, 1.06) p=.095		0.62 (0.35, 1.08) p=.092		0.96 (0.39, 2.41) p=.938	
Odds of overall improvement on the NIAID OS evaluated at Day 15										
N	509	507	70	69	273	283	111	103	55	52
OR (95% CI) p-value[e]	1.26 (1.01, 1.58) p=.041		0.54 (0.28, 1.03) p=.063		1.21 (0.89, 1.65) p=.222		2.20 (1.36, 3.57) p=.001		1.78 (0.86, 3.69) p=.120	
All-cause mortality Day 29, overall										
N	509	507	70	69	273	283	111	103	55	52
Number of deaths, n (%)	37 (7.3)	23 (4.5)	0	0	12 (4.4)	5 (1.8)	13 (11.7)	7 (6.8)	12 (21.8)	11 (21.2)
HR[f] (95% CI) p-value	0.63 (0.37, 1.05) p=.075[b]		NR		0.40 (0.14, 1.14) p=.075		0.55 (0.22, 1.38) p=.198		0.91 (0.40, 2.07) p=.828	
KM estimate, % (95% CI)	8 .2, 10.8)	4.9 (2.8, 7.6)	0	0	4.7 (2.5, 8.7)	1.9 (0.4, 5.0)	13.0 (6.1, 22.2)	7.5 (2.2, 16.5)	2.6 12.3, 39.6)	21.6 (8.0, 36.1)

Abbreviations: n = number of patients in specified category; N = number of patients in the specified treatment group, disease severity, and analysis population; NR = not reached; OR = odds ratio; OS = ordinal scale.

c Those who died or required noninvasive ventilation/high-flow oxygen or invasive mechanical ventilation.

d p-value was calculated using logistic regression with disease severity as a model covariate.

e p-value was calculated using proportional odds model with disease severity as a model covariate.

f HR is the ratio of the hazard of time to death in each treatment group estimated from the Cox model. The ratio is BARI + RDV to PBO + RDV. Hazard ratio for the "Overall" group is the HR from the stratified Cox model.

CHMP's assessment

The results of the secondary outcome measures by baseline ordinal scale further support that for patients in baseline OS categories 5 and 6, benefit from baricitinib treatment can be observed. A benefit was suggested in terms of the Proportion of patients progressing to ventilation or death through Day 29 (not statistically significant), Odds of overall improvement on the NIAID OS evaluated at Day 15 (only statistically significant for baseline OS6 patients), and All-cause mortality at Day 29 (not statistically significant). No conclusions can be drawn for patients with baseline OS 4, due to the low number of patients included in baseline OS 4 and low numbers of baseline OS 4 patients who progressed to ventilation. No patients with baseline OS 4 died in this study. For baseline OS 7, there was no clear effect

of baricitinib on the proportion of patients progressing to ventilation or death through Day 29 and on All-cause mortality Day by 29 based on the ORs of 0.96 and 0.91. A higher OR was observed for Odds of overall improvement on the NIAID OS evaluated at Day 15 (1.78 in favour of baricitinib); however, this was based on a very limited subset of patients with baseline OS 7 (52 and 55 in baricitinib and placebo arms).

Additional and exploratory analyses

Time to recovery was also explored within **prior remdesivir treatment subgroups** (Any Prior Treatment versus No Prior Treatment). There were 949 subjects with no prior remdesivir treatment (Baricitinib + RDV group: 476 subjects; Placebo + RDV group: 473 subjects) and 84 subjects with some prior remdesivir treatment (Baricitinib + RDV group: 39 subjects; Placebo + RDV group: 45 subjects). Among subjects with no prior remdesivir treatment, the hazard of recovery increases by 21% (HR 1.21; 95% CI: 1.05, 1.40) in the Baricitinib + RDV arm compared to the Placebo + RDV arm. The hazard of recovery decreases by 19% in subjects with prior remdesivir treatment (HR 0.81; 95% CI: 0.50, 1.32) in the baricitinib + RDV arm relative to Placebo + RDV.

An ad hoc sensitivity analysis for time to recovery by treatment group was also performed for **subgroups with corticosteroid and dexamethasone use**. Table 18 depicts the median time to recovery in days, for subjects receiving corticosteroids or dexamethasone by baseline ordinal scale.

Table 18 Median time to recovery for subjects who received corticosteroids / dexamethasone

		Barcitinib+RDV	**Placebo+RDV**	**Proportion of subjects that received corticosteroids / dexamethasone post enrolment**
Baseline OS4	Any time corticosteroids	4 days (95% CI: 2.0, 8.0)	5.5 days (95% CI: 2.0, 10.0)	
	Post enrolment corticosteroids	2 days (95% CI: N.e.)	2 days (95% CI: N.e.)	1.4% in both treatment groups received corticosteroids. No subjects in baseline ordinal score 4 received dexamethasone post enrolment.
Baseline OS5	Any time corticosteroids	9 days (95% CI:7.0, 12.0)	9 days (95% CI: 6.0,16.0)	
	Post enrolment corticosteroids	15 days (95% CI: 11.0, N.e.)	13.5 days (95% CI: 7.0, N.e.)	10.1% in the Bari+RDV group 9.4% in the PBO+RDV group
	Post enrolment dexamethasone	16 days (95% CI: 10.0, N.e.)	11.0 days (95% CI: 7.0, 27.0)	6.9% in the Bari+RDV group 6.5% in the PBO+RDV group
Baseline OS6	Any time corticosteroids	25 days (95% CI: 10.0, N.e.)	27 days (95% CI: 20.0, N.e.)	
	Post enrolment corticosteroids	N.e. (95% CI: 9.0, N.e.)	N.e. (95% CI: 22.0, N.e.)	11.7% in the Bari+RDV group 21.2% in the PBO+RDV group
	Post enrolment dexamethasone	20.5 days (95% CI: 9.0, N.e.)	N.e. (95% CI: 17.0, N.e.)	5.8% in the Bari+RDV group 11.5% in the PBO+RDV group
Baseline OS7	Any time corticosteroids	N.e. (95% CI: 25.0, N.e.)	27 days (95% CI: 24.0, N.e.)	
	Post enrolment corticosteroids	N.e. (95% CI: 25.0, N.e.)	N.e. (95% CI: 24.0, N.e.)	25.9% in the Bari+RDV group 28.1% in the PBO+RDV group
	Post enrolment dexamethasone	N.e. (95% CI: 16.0, N.e.)	N.e. (95% CI: 15.0, N.e.)	9.3% in the Bari+RDV group 10.5% in the PBO+RDV group

N.e.: Not estimable

CHMP's assessment

When this study was performed, corticosteroids were not used as SOC for the treatment of COVID-19, reflected by the small numbers of patients who received corticosteroids in the ACTT-2. This hampers any conclusions on the simultaneous use of baricitinib and corticosteroids in this study. Information on the simultaneous use of corticosteroids will mainly come from the results of the KHAA and RECOVERY study discussed below.

Notably, the largest difference in corticosteroid use between the baricitinib and placebo groups was observed for baseline OS 6, with more patients in the placebo group receiving corticosteroids/dexamethasone post-baseline. It is unknown if more patients in the placebo group received corticosteroids because of their potentially worse clinical status as compared to patients who had received baricitinib for some days.

Of note, the median time to recovery seemed longer in baseline OS 5 patients in the baricitinib group. Given the low number of subjects in this comparison, no conclusions can, however, be drawn. An exploratory objective was to evaluate **virologic efficacy** by assessment of percent of patients with a detectable oropharyngeal sample, quantitative oropharyngeal sample, development of resistance at Days 3, 5, 8, 11, 15, 29 or quantitative sample in blood at Days 3, 5, 8 and 11. The results have not been presented in the CSR.

CHMP's assessment

The MAH is requested to provide the virologic efficacy data. (**OC**)

KHAA/COV-BARRIER

Methods

Study KHAA was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of baricitinib 4 mg QD. The study was divided into 3 periods, conducted over approximately 60 days:

- Period 1, Screening: occurred on Day 1 prior to receiving first dose of study medication
- Period 2, Treatment: Treatment was administered for up to 14 days. This was followed by treatment evaluations up to Day 28.
- Period 3, Follow-up: Period started after the treatment period, with a follow-up visit at approximately 28 days after the last dose of the study drug, and an additional follow-up visit at approximately Study Day 60.

Study participants

Patients eligible for **inclusion** were male or non-pregnant female adults ≥ 18 years of age at time of enrolment, who:

- Were hospitalised with COVID-19, and had confirmed SARS-CoV-2 infection as determined by PCR or other commercial or public health assay in any specimen, as documented by either of the following:
    - PCR positive in sample collected < 72 hours prior to randomization; OR
    - PCR positive in sample collected ≥ 72 hours prior to randomization, documented inability to obtain a repeat sample (e.g. due to lack of testing supplies, limited testing capacity, results taking > 24 hours, etc) AND progressive disease suggestive of ongoing SARS-CoV-2 infection.
- Require supplemental oxygen at the time of study entry and at randomization (Note: This inclusion criterion was amended in KHAA protocol (d), based on data from the ACTT-2 study. Prior to this, the patients in the OS 4 category were eligible to participate in this study).
- Have indicators of risk of progression: at least 1 inflammatory markers >ULN (CRP, D-dimer, LDH, ferritin) with at least 1 instance of elevation >ULN within 2 days before study entry.

Patients meeting any of the following criteria were **excluded from participation**:

- Were receiving cytotoxic or biologic treatments, T-cell- or B-cell-targeted therapies, interferon, or JAK inhibitors for any indication at study entry.
- Had ever received convalescent plasma or intravenous immunoglobulin for COVID-19.
- Had received high-dose corticosteroids at doses >20 mg per day (or prednisone equivalent) administered for ≥14 consecutive days in the month prior to study entry.
- Had received neutralizing antibodies, such as bamlanivimab, casirivimab, and imdevimab, for COVID-19.
- Required invasive mechanical ventilation, including ECMO at study entry (Note: Per the protocol, patients were excluded if they required invasive mechanical ventilation, including ECMO, at study entry (NIAID OS 7). Based on FDA feedback, a protocol addendum, approved 01 December 2020, modified the inclusion and exclusion criteria to allow a selected number of countries to enrol patients at NIAID OS 7. The addendum will enrol approximately 100 patients (50 per treatment arm) and will evaluate the efficacy and safety of baricitinib + SOC compared to placebo + SOC in exploratory analyses. The addendum is ongoing, and no data are available to date).

CHMP's assessment

Different literature reports conclude on the association of elevated inflammatory markers and severe COVID-19. By adding this inclusion criterion, the MAH has attempted to enrol a population more likely to contribute to the primary outcome, which is considered acceptable. During the study, the inclusion criteria changed based on data from the ACTT-2 study. As a result, some patients who originally were eligible for enrolment were no longer eligible (baseline OS 4 patients). Given that these patients are also not captured in the proposed indication, this does not impact the overall conclusions.

Overall, the in- and exclusion criteria are considered to be appropriate and to result in a population representative for the adult population envisioned.

Treatments

Patients received oral baricitinib 4 mg or placebo once daily for 14 days or up to hospital discharge, whichever occurred first.

Objectives

Primary objective: To evaluate the effect of baricitinib 4-mg once daily (QD) compared to placebo on disease progression in patients with COVID-19 infection.

Secondary objective: To evaluate the effect of baricitinib 4-mg QD compared to placebo on clinical outcomes in patients with COVID-19 infection.

Outcomes/endpoints

The **primary endpoint** of the KHAA study was the proportion of patients progressing to ventilation or death by Day 28. Disease progression was defined as an increase in NIAID OS:

- *from* baseline OS 4 or 5 *to* OS 6, 7, or 8, or
- *from* baseline OS 6 *to* OS 7 or 8.

The primary endpoint was analysed in two populations:

- Population 1: all randomised patients
- Population 2: patients who, at baseline, require oxygen supplementation and are not receiving dexamethasone or other systemic corticosteroids for the primary study condition

The analysis of the primary endpoint does not differentiate outcomes subsequent to the progression.

The **secondary endpoints** of the KHAA study were:

- Time to recovery, where recovery is defined as clinical status in states 1, 2, or 3 of the 8-point ordinal scale, censored at Day 28
- Overall improvement on the NIAID-OS evaluated at Day 4, Day 7, Day 10, and Day 14
- All-cause mortality (Day 1 to Day 28)
- Proportion of patients with 1-point improvement or live discharge by Day 4, Day 7, Day 10, and Day 14
- Number of ventilator free days (Day 1 to Day 28)
- Proportion of patients with at least 2-point improvement on the NIAID-OS or live discharge from the hospital, Days 4, 7, 10, 14, 21, and 28

CHMP's assessment

The primary endpoint of disease progression is considered to be clinically relevant. However, by its current definition, it only considers the first event of disease progression and does not provide information on what happened to patients after this first event.

As described under ACTT-2, time to recovery is not considered a very robust endpoint as it may depend on several factors (e.g. differentiation between OS 3 and 4 or relapse after initial recovery). The clinical relevance of time to recovery could be debated for these reasons, and time to sustained recovery would have been preferred.

The same applies to the proportion of patients with a one-point change in ordinal scale or discharge, as one point improvement could depend on the estimation of the individual clinician and deterioration can occur after initial improvement.

Sample size

With the last protocol amendment (amendment) the sample size was updated to approximately 1400 patients based on the blinded review of the proportion of patients requiring oxygen supplementation without the use of dexamethasone or systemic corticosteroids at baseline and the potential that concomitant use of systemic corticosteroids may reduce the magnitude of the treatment effect. Table 19 describes the power calculations for various scenarios with a total sample size of 1400. This assumes, for illustration, that α1 for Population 1 is 75% of the total alpha and that 60% of the patients were taking dexamethasone or other corticosteroids at baseline. Amendment e also allowed for the sample size to be increased using an unblinded sample size re-estimation during an interim analysis (that occurred in January 2021).

Table 19 Power calculations for various scenarios with a total sample size of 1400

Treatment Effect Size in Patients Who are at OS 5 or OS 6 at Baseline		Combined Effect Size	Power for at Least One of the Two Primaries to Succeed
Patients using dexamethasone or a systemic corticosteroid	Patients not using dexamethasone or a systemic corticosteroid		
0.075	0.075	0.075	81%
0.040	0.075	0.054	54%

Abbreviations: NIAID = National Institute of allergy and Infectious Diseases; OS 5 = #5 on the 8-point NIAID ordinal scale - Hospitalized, requiring supplemental oxygen; OS 6 = #6 on the 8-point NIAID ordinal scale – Hospitalized, on noninvasive ventilation or high-flow oxygen devices.

CHMP's assessment

The general strategy for the sample size re-assessment based on conditional power from an unblinded interim analysis is acceptable.

Some clarification has been requested concerning the sample size re-estimation (SSR) procedure. The MAH clarified that the square root of the chi-square statistic was used for the conditional power calculation and not the original statistic as mentioned in the SAP. However, the square root of the chi-square statistic would still be inadequate for the conditional power to be properly calculated. The latter would require the original Wald statistic (the square of which equals the chi-square statistic). It is thus further assumed that the sign of the statistic was also available (given that the interim sample size re-estimation was unblinded). Since this observation is not expected to have a substantial impact on the outcome of the study, this issue is not further pursued.

Randomisation

Patients were randomized 1:1 to receive baricitinib or placebo. Randomisation was stratified by:

- disease severity (OS 4 [not on supplemental oxygen], OS 5 [those on low flow oxygen devices, by prongs or mask], and OS 6 [noninvasive ventilation/high-flow oxygen devices]),
- age (younger than 65 years; 65 years or older),
- region (US, Europe, and rest of the world), and
- dexamethasone and/or other systemic corticosteroid used at baseline for primary study condition (Yes or No).

Blinding (masking)

Study KHAA is a double-blind study. Patients, investigators, and all other personnel involved in the conduct of the study remained blinded to individual treatment assignments for the duration of the study. The sponsor remained blinded during the interim analysis for the DMC and was unblinded only at the time of the primary outcome database lock.

Statistical methods

Analysis populations

The following analysis populations were defined (see Table 20):

Table 20 Analysis populations KHAA

Population	Description
Entered	All participants who sign the informed consent form
Intent-to-Treat (ITT)	All participants randomly assigned to study intervention. Participants will be analyzed according to the intervention to which they were assigned.
Per Protocol Set (PPS)	The PPS will include those participants in the ITT population who do not have any identified important protocol violations considered to impact efficacy analyses. Qualifications for, and identification of, significant or important protocol violations will be determined while the study remains blinded, prior to database lock.
Safety	All participants randomly assigned to study intervention and who receive at least 1 dose of study intervention and who did not discontinue from the study for the reason 'Lost to Follow-up' at the first postbaseline visit. Participants will be analyzed according to the intervention they actually received.
Follow-up	All randomized participants who received at least 1 dose of investigational product and have entered the post-treatment follow-up period. Participants will be analyzed according to the intervention to which they received.

Primary Analysis

The primary comparison of interest is the proportion of patients who die or require non-invasive ventilation/high-flow oxygen or invasive mechanical ventilation (including ECMO) by Day 28. The primary comparison will be performed on two different populations:

Population 1 – all randomized patients

Population 2 – patients who, at baseline, require oxygen supplementation and are not receiving dexamethasone or other systemic corticosteroids for the primary study condition.

Patients on non-invasive ventilation/high-flow oxygen at baseline would be counted toward this endpoint if they progressed to invasive mechanical ventilation. Treatment comparisons between baricitinib 4-mg QD + background therapy and placebo + background therapy will be made using logistic regression with baseline stratification factors and treatment group in the model.

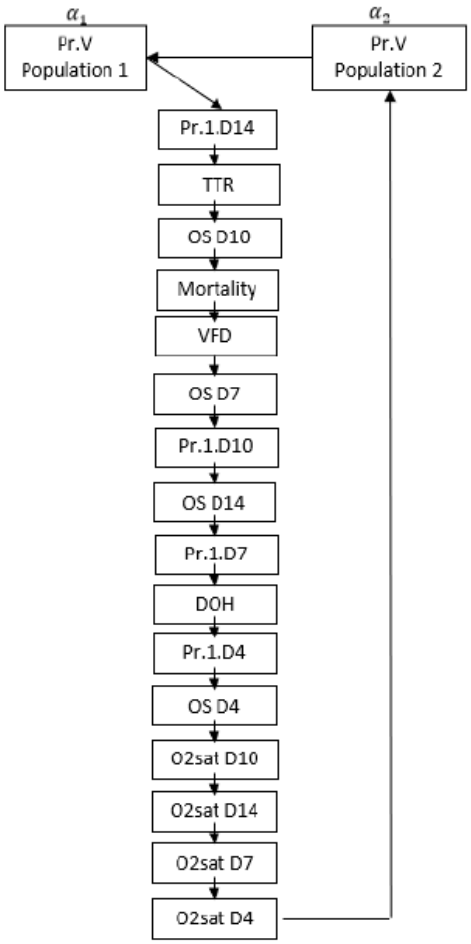
For patients who start with ventilation at baseline, the patients need to be worsening in symptom (at least 1-point worsening in NIAID-OS) to be counted.

For the primary comparison involving two different populations, the alpha will be split between the two populations such that 99% of alpha is assigned to Population 1 and the rest to Population 2. The primary endpoint will be met if any one or both of these two populations show a significant treatment effect.

Multiple Comparisons/Multiplicity

Multiplicity controlled analyses will be performed on the primary and key secondary endpoints to control the overall family-wise Type I error rate at a 1-sided α level of 0.025. The graphical multiple testing procedure is displayed below (Figure 7).

Figure 7 Graphical testing scheme



Abbreviations: Pr.V: Proportion of patients who die or require non-invasive ventilation/high-flow oxygen or invasive mechanical ventilation (including ECMO) by Day 28.
TTR: Time to recovery, where recovery is defined as clinical status in states 1, 2, or 3 of the 8-point ordinal scale, censored at Day 28.
Pr.1.D4/7/10/14: proportion of patients with at least 1-point improvement on the NIAID-OS or live discharge from the hospital at Day 4, Day 7, Day 10, and Day 14.
VFD: number of ventilator-free days (Day 1 to Day 28). OS D4/7/10/14: overall improvement on the NIAID-OS evaluated at Day 4, Day 7, Day 10, and Day 14. DOH: duration of hospitalization (Day 1 to Day 28).
O2sat D4/7/10/14 proportion of patients with a change in oxygen saturation from <94% to ≥94% from baseline to Day 4, Day 7, Day 10, Day 14. Mortality: All-cause mortality (Day 1 to Day 28).

CHMP's assessment

Methods for the analysis of the primary outcome and multiplicity correction are acceptable. Of note, and in combination with the comments in the sample size section, the MAH was planning on assessing efficacy on a one-sided 2.5% significance levels, but in the CSR two-sided p-values are presented.

Handling of Dropouts or Missing Data

The following imputation rules will be used for subjects who are lost to follow-up, withdrew from the study early, or do not have further outcome data available after discharge for any reason or death.

- Infinite Event Time Imputation (IETI)

For some time-to-event endpoints, if there are competing risks to the event of interest, then the event times censored due to the competing risk will be imputed as infinite. This imputation method will be applied if the event of interest is in the opposite direction of death (e.g., recovery or improvement). For

time to recovery or time to improvement, all deaths within 28 days will be considered censored at Day 28 with respect to time to event of interest. Conceptually, a death corresponds to an infinite time to event of interest, but censoring at anytime greater than or equal to Day 28 gives the same answer as censoring at Day 28; both correspond to giving death the worst rank.

- Last Observation Carried Forward (LOCF)

Some analyses (in particular for quantitative or ordinal scale measures) will use the LOCF approach. Intermittent or terminally missing data will be filled in by carrying forward the last available measurement prior to the missing data. This methodology will only be utilized for patients who had both a baseline and a postbaseline measurement

- Multiple Imputation

A multiple imputation method will be used to impute the missing NIAID-OS scores (Rubin, 1996). The multiply-imputed datasets will be used for the primary analyses of several endpoints involving the NIAID-OS scores. A total of 100 multiply-imputed datasets will be generated. For random number generation, the seed will be set 3012021. The multiple imputation will be performed in a stratified manner with the imputation performed separately for each of the following levels: (1) baricitinib patients with baseline NIAID-OS of 5 or 6 and baseline steroid use, (2) baricitinib patients with baseline NIAID-OS of 5 or 6 and no baseline steroid use, (3) other baricitinib patients, (4) comparator patients with baseline NIAID-OS of 5 or 6 and baseline steroid use, (5) comparator patients with baseline NIAID-OS of 5 or 6 and no baseline steroid use, and (6) other comparator patients. These strata are slightly reduced from what might be expected in order to keep a sufficient number of patients in each stratum. Imputation will be performed using a Markov model where each transition to a future state is dependent on only the previous state. This approach is described in detail in Appendix 2. The intended estimand for the multiple imputation approach is based on the treatment policy strategy for handling intercurrent events (ICH E9R [ICH 2017]). In this strategy the value of the NIAID-OS score is the value of interest regardless of any intercurrent events that occurred. The NIAID-OS includes a state for death, and thus it is meaningful even for patients who have died.

CHMP's assessment

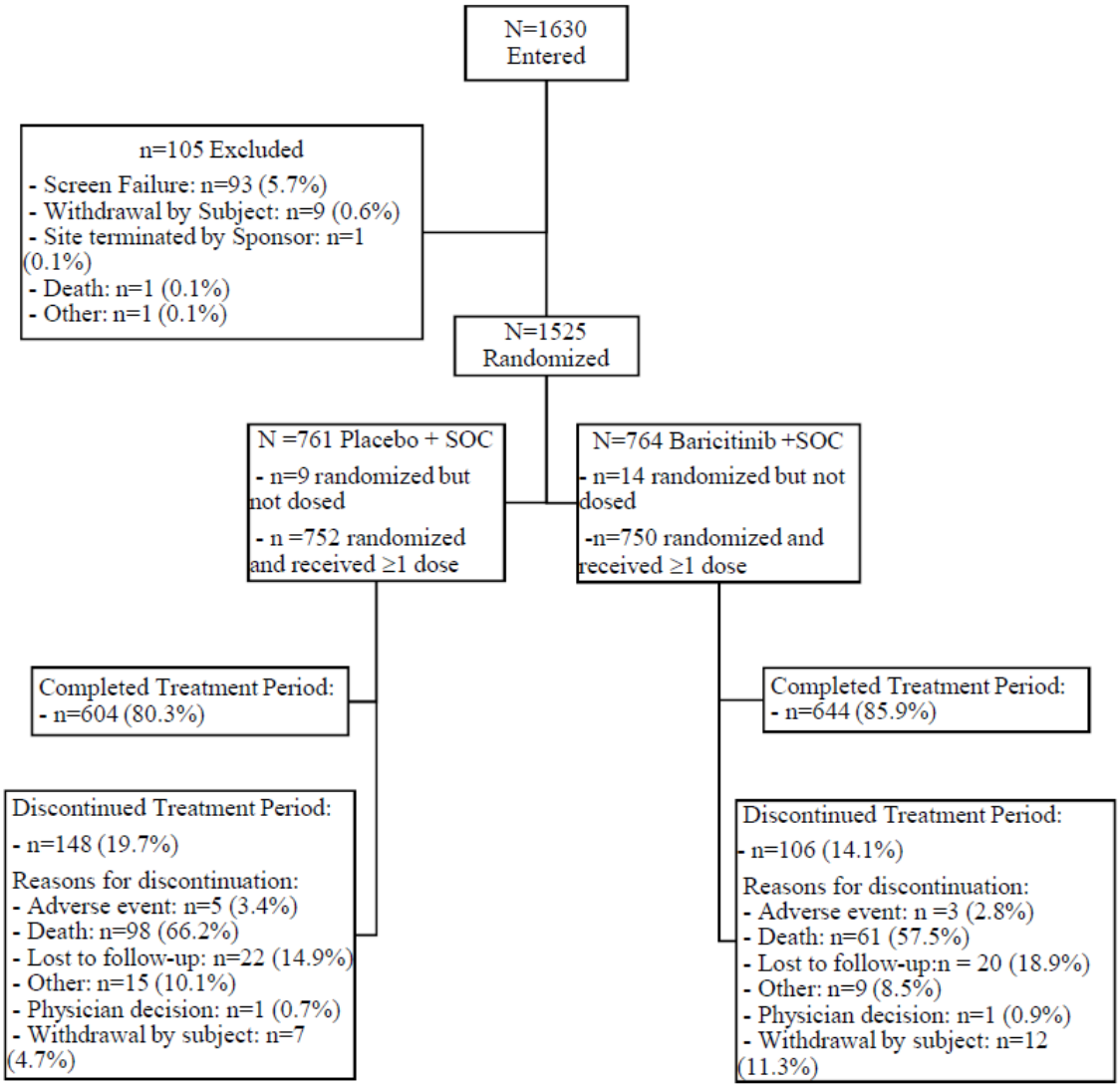
The treatment policy estimand is endorsed. Given the limitations of LOCF and the challenges of MI described in Appendix 2 of the SAP and the novel approach employed (Markov model multiple imputation - MMMI), the MAH has been requested to provide a summary table with patient disposition on a day-by-day summary fashion, in order for the amount of missing/imputed values to be assessed. Patient disposition on a day-by-day fashion has been provided (data not shown here). Approximately 90% of patients was still ongoing at Day 14 and approximately 83% at Day 28. The most common reason for study discontinuation was death (Study Day 6 onward) or withdrawal by subject (Study Days 1 through 5). Other reasons for study discontinuation included physician decision, adverse event, and lost to follow-up. At Day 28, less patients in the baricitinib arm than in the placebo arm permanently discontinued 15.2% vs 18.9%.

It was understood from the notation used in Appendix 2 that death (OS=8) was also a possible imputation value in the MMMI model. Given that the comparison of mortality rates is a key outcome for the assessment, the MAH has been requested to provide the number and proportion of deaths (OS=8) that were imputed, as it was unclear whether the Log-Rank test was based on the MMMI-imputed dataset. The MAH clarified that the main analysis was based on the standard imputation imposed by the KM model and was not based on the MMMI-imputed dataset, which is acceptable.

Results

Participant flow

Figure 8 Subject disposition KHAA



A total of 1630 patients entered the study (Figure 8). 93 patients did not meet in- or exclusion criteria. A total of 1525 patients were randomly assigned to treatment. Of patients randomized, 23 did not receive a dose of study treatment for eligibility reasons (placebo = 9; baricitinib = 14); 604 subjects (80.3%) of placebo + SOC-treated patients and 644 subjects (85.9%) of baricitinib + SOC-treated patients completed the treatment period with follow-up visits scheduled 28 days after the last dose of study drug, and another follow-up visit at approximately Day 60 for eligible/consented patients.

Recruitment

The study was conducted at 101 centres located in Argentina, Brazil, Germany, India, Italy, Japan, Korea, Mexico, Russia, Spain, the UK and the US. Date of first enrolment 11 Jun 2020; Date of last visit (Day 28): 12 Feb 2021. The analyses presented in this report are based on a database lock date of 23 March 2021.

Conduct of the study

Protocol deviations

204 (13.4%) patients had ≥ 1 important protocol deviation. Protocol deviations occurred in 12.9% of patients in the placebo + SOC group and 13.9% of patients in the baricitinib + SOC group. Important protocol deviations are listed in Table 21.

Table 21 Protocol deviations KHAA

Protocol Deviation Category	No. of Patients in the Category	Characterization of Events	Description of Situation
Informed Consent	6	Improper consent	NA[a]
		Informed consent not obtained	No reconsent for safety update
Eligibility	23	Inclusion/Exclusion	• 4 patients: SARS-CoV-2 infection not confirmed as defined in the protocol • 14 patients: Have ALT or AST >5 x ULN • 4 patients: Not on supplemental oxygen at the time of study entry and randomization[b] • 2 patients: Receiving biologic treatment, anti-IL-6, T- or B-cell therapy, interferon, or JAK inhibitors
Investigational Product	99	Dosing error	• 12 patients: IP not interrupted when criteria were met • 42 patients: Incorrect dose or frequency of study drug • 2 patients: NA[a] • 16 patients: randomized to 4 mg with eGFR <60 and does not have dose adjusted to 2 mg • 3 patients: received IP after being discharged from the hospital • 3 patients: received IP for longer than 14 days
		Other	• 1 patient: NA[a]
		Treatment assignment/Randomization error	• 10 patients: IWRS data entry errors impacting patient randomization • 8 patients: NA[a] • 7 patients: dispensed incorrect IP
Study Procedures	69	Excluded concomitant medications	• 1 patient: received any biologic therapy, IL-6, T-cell or B-cell therapies, JAK inhibitor, or IgG
		Lab/imaging criteria	• 66 patients: imaging not done at Visit 1 or within allowed timelines
		Violation of discontinuation criteria	• 2 patients: not permanently discontinued when criteria were met
Safety	26	SAEs	• 26 patients: SAEs not reported in 24 hours

Protocol amendments

Changes in study conduct are summarised in Table 22.

Table 22 Summary of Protocol Amendments

Protocol	Approval Date	Substantial (Yes/No)	Key Changes
KHAA	18 May 2020	N/A	
KHAA(a)	27 May 2020		• Changes made to primary endpoint and wording of primary objective in response to FDA feedback • Added secondary endpoint in response to FDA feedback • Removed references to the internal assessment committee
KHAA(b)	03 Jun 2020	Yes	• Updated the primary endpoint in response to FDA feedback • Added statement regarding concomitant use of hydroxychloroquine and chloroquine • Addition of Exclusion Criteria 25 and 26
KHAA(c)	12 Aug 2020	Yes	• Increased sample size to a range of 600 to 1000 participants, to accommodate evolving changes in SOC therapy • Revised number of patients to be randomized, power, and assumptions for the power calculation • Clarification of Exclusion Criterion 8 regarding corticosteroid use
KHAA(d)	20 Oct 2020	Yes	• Added the Day-60 assessment in the follow-up period and increased total maximum study duration • Increased sample size to 1000 participants • Added sample size re-estimation considerations of interim analyses • Revised protocol Inclusion Criterion 4
KHAA(e)	25 Nov 2020	Yes	• Added a subpopulation to the primary endpoint to evaluate disease progression in patients requiring oxygen supplementation without use of dexamethasone or systemic corticosteroids at baseline • Increased sample size to approximately 1400 participants • Added Exclusion Criterion 27 regarding neutralizing antibodies • Updated statistical methods in line with changes made to the primary endpoint

Baseline data

For Study KHAA, demographics and baseline characteristics were similar between the baricitinib + SOC and placebo + SOC groups (

Table 23). Most patients were male (63.1%) between 40 to 64 years of age (55.6%) with a mean age of 57.6 years; 32.7% were aged 65 years or over. The majority were white (61.6%), and most were overweight (mean BMI = 30.5 kg/m2). The majority of patients had symptom onset of 7 days or more (69.0%). Baseline clinical status was similar between the 2 treatment groups: 370 patients (24.4%) had a clinical status of 6, 962 patients (63.4%) had a clinical status of 5, and 186 patients (12.3%) had a clinical status of 4.

Table 23 Summary of Baseline Demographic Characteristics KHAA-ITT Population

Demographic Parameter		Placebo (N=761)	Baricitinib-4mg-QD (N=764)	Total (N=1525)
Sex n(%)	n	761	764	1525
	F	288 (37.8)	274 (35.9)	562 (36.9)
	M	473 (62.2)	490 (64.1)	963 (63.1)
Age (yrs)	n	761	764	1525
	Mean (SD)	57.5 (13.8)	57.8 (14.3)	57.6 (14.1)
	>=65 years	243 (31.9)	256 (33.5)	499 (32.7)
Race n(%)	n	741	752	1493
	American Indian or Alaska Native	168 (22.7)	148 (19.7)	316 (21.2)
	Asian	94 (12.7)	80 (10.6)	174 (11.7)
	Black or African American	36 (4.9)	39 (5.2)	75 (5.0)
	Multiple	1 (0.1)	2 (0.3)	3 (0.2)
	Native Hawaiian or Other Pacific Islander	2 (0.3)	3 (0.4)	5 (0.3)
	White	440 (59.4)	480 (63.8)	920 (61.6)
	Missing	20	12	32
Weight (kg)	n	745	744	1489
	Mean (SD)	86.26 (20.94)	86.54 (20.81)	86.40 (20.86)
BMI (kg/m2)**	n	744	740	1484
	Mean (SD)	30.6 (6.6)	30.4 (6.4)	30.5 (6.5)
Country n(%)	n	761	764	1525
	Argentina	101 (13.3)	107 (14.0)	208 (13.6)
	Brazil	165 (21.7)	172 (22.5)	337 (22.1)
	Germany	11 (1.4)	9 (1.2)	20 (1.3)
	India	31 (4.1)	19 (2.5)	50 (3.3)
	Italy	10 (1.3)	15 (2.0)	25 (1.6)
	Japan	19 (2.5)	19 (2.5)	38 (2.5)
	Korea, Republic of	20 (2.6)	16 (2.1)	36 (2.4)
	Mexico	143 (18.8)	138 (18.1)	281 (18.4)
	Puerto Rico	3 (0.4)	8 (1.0)	11 (0.7)
	Russian Federation	54 (7.1)	58 (7.6)	112 (7.3)
	Spain	42 (5.5)	45 (5.9)	87 (5.7)
	United Kingdom	7 (0.9)	4 (0.5)	11 (0.7)
	United States	155 (20.4)	154 (20.2)	309 (20.3)
Geo Region n(%)	n	761	764	1525
	Europe	70 (9.2)	73 (9.6)	143 (9.4)
	Rest of World	533 (70.0)	529 (69.2)	1062 (69.6)
	United States	158 (20.8)	162 (21.2)	320 (21.0)
Baseline NIAID OS		756	762	1518
	4	97 (12.8)	89 (11.7)	186 (12.3)
	5	472 (62.4)	490 (64.3)	962 (63.4)
	6	187 (24.7)	183 (24.0)	370 (24.4)
Prior therapy of interest, n(%)	n	761	764	1525
	NSAIDs	53 (7.0)	61 (8.0)	114 (7.5)
	Antivirals	61 (8.0)	60 (7.9)	121 (7.9)
	Antibiotics	128 (16.8)	137 (17.9)	265 (17.4)
	Immunosuppressants	2 (0.3)	0	2 (0.1)
	Anti-malarials	9 (1.2)	8 (1.0)	17 (1.1)
	Corticosteroids	94 (12.4)	97 (12.7)	191 (12.5)
Symptom onset	n	591	601	1192
	<7 days	176 (29.8)	194 (32.3)	370 (31.0)
	≥7 days	415 (70.2)	407 (67.7)	822 (69.0)
Renal function status, n(%)	n	718	715	1433
Impaired		90 (12.5)	90 (12.6)	180 (12.6)
Not impaired		628 (87.5)	625 (87.4)	1253 (87.4)

N = number of subjects in population; n = number of subjects with non-missing data in the specified category

99.7% of patients had comorbidities at enrolment (99.5% for placebo and 99.9% for baricitinib groups respectively). The most commonly reported comorbidities were hypertension (47.9%), obesity (33.0%), and diabetes mellitus (Type I and Type II, 30.0%).

CHMP' assessment

Baseline characteristics were well balanced between the two arms of the study. Although there was a tendency toward longer symptom duration before enrolment in the study in the placebo group, the baseline clinical status (as based on OS) was comparable for both study arms.

Concomitant medication

Previous medications used for COVID-19 included dexamethasone in 5.1% (4.5% in placebo and 5.8% in baricitinib arms, respectively) and remdesivir in 4.1% (4.3% in placebo and 3.9% in baricitinib arms, respectively). Overall, 79.3% of the patients in Study KHAA received systemic corticosteroids at baseline (Table 24).

Most of these patients (91.3%) received dexamethasone. The use of systemic corticosteroids at baseline was well balanced between treatment groups (PBO + SOC 78.3% vs BARI + SOC 80.3%).

Approximately 19% of patients received remdesivir at baseline. This was well balanced between treatment groups (PBO + SOC 19.4% vs BARI + SOC 18.4%).

Prophylaxis for VTE was required unless contraindicated. Enoxaparin was the most commonly utilized medication, which was used by 73% of the patients

Table 24 Concomitant use of corticosteroids and remdesivir, KHAA

Baseline Attribute	PBO + SOC (N = 761)	BARI 4 mg + SOC (N = 764)	Total (N = 1525)
Steroid Use, n (%)			
Yes	592 (78.3)	612 (80.3)	1204 (79.3)
Dexamethasone Use	533 (90.0)	566 (92.5)	1099 (91.3)
No	164 (21.7)	150 (19.7)	314 (20.7)
Remdesivir Use, n (%)			
Yes	147 (19.4)	140 (18.4)	287 (18.9)
No	609 (80.6)	622 (81.6)	1231 (81.1)

Treatment compliance

Mean treatment exposure was 8.3 days in the placebo group vs 8.1 days in the baricitinib group. Treatment was discontinued in 148/752 (19.7%) patients in the placebo group and 106/750 (14.1%) in the baricitinib group. Most common reasons for discontinuations were death (66.2% vs 57.5% in placebo and baricitinib groups respectively) loss to follow-up (14.9% vs 18.9%), other (10.1% vs 8.5%), withdrawal by subject (4.7% vs 11.3%) (please also refer to Figure 8).

Numbers analysed

The ITT Population includes 1525 patients, 761 in the placebo + SOC group and 764 in the baricitinib + SOC group. The Safety Population (all patients who received at least one dose of study treatment) includes 1502 patients, 752 in the placebo + SOC group and 750 in the baricitinib + SOC group.

The primary endpoint was analysed in Population 1 (all randomised patients) and Population 2 (patients who, at baseline, require oxygen supplementation and are not receiving dexamethasone or other systemic corticosteroids for the primary study condition). Population 2 totalled only 205 patients (13.4% of the ITT Population).

Outcomes and estimation

Primary efficacy endpoint

The primary endpoint reflects any event of progression or death. This endpoint does not differentiate outcomes subsequent to the progression. Patients who progressed and survived, including those who subsequently recovered, were given the same weight in the primary analysis as patients who died.

In both Populations 1 and 2, there was not a statistically significant difference in the proportion of patients who died or progressed to require ventilation between the baricitinib + SOC and placebo + SOC groups.

Although not statistically significant, numerical differences were observed in the proportion of patients who progressed in the baricitinib + SOC group compared with the placebo + SOC group.

- In Population 1, overall 2.7% less patients progressed in the baricitinib + SOC group compared with the placebo + SOC group. A similar magnitude of effect was observed within each baseline OS subset, see Table 25.
- In Population 2 (N = 205), patients requiring oxygen supplementation who did not receive baseline corticosteroids, 1.7% more patients progressed in the baricitinib + SOC group compared with the placebo + SOC group (28.9% vs 27.1%).

Table 25 Summary KHAA Results for the Primary Outcome Measure by Treatment Group by Ordinal Score at Baseline, ITT Population

	Overall		**Baseline OS 4 (No supplemental oxygen)**		**Baseline OS 5 (Low-flow oxygen)**		**Baseline OS 6 (Noninvasive ventilation or high-flow oxygen)**	
	Placebo	Baricitinib	Placebo	Baricitinib	Placebo	Baricitinib	Placebo	Baricitinib
Proportion of patients progressing to ventilation or death through Day 28[a] (Population 1: Overall population)								
N	756	762	97	89	472	490	187	183
Estimate % (95% CI)	30.5 (27.2, 33.8)	27.8 (24.6, 31.0)	9.5 (3.6, 15.4)	7.0 (1.6, 12.3)	28.3 (24.3, 32.4)	25.6 (21.7, 29.5)	46.8 (39.6, 54.0)	43.8 (36.5, 51.1)
OR (95% CI) p-value[b]	0.85 (0.67, 1.08) p=.180		0.78 (0.27, 2.22) p=.640		0.87 (0.65, 1.17) p=.352		0.85 (0.56, 1.30) p=.459	

[a] Those who died or required noninvasive ventilation/high-flow oxygen or invasive mechanical ventilation.

[b] p-value was calculated using logistic regression adjusted for baseline disease severity, age, region, and systemic corticosteroids used at baseline for primary study condition.

CHMP's assessment

KHAA failed to meet its primary endpoint of risk of progression to ventilation or death by Day 28. As a consequence, secondary endpoints were not multiplicity controlled.

The MAH has been requested to clarify the discrepancy in the numbers presented for the patients in the specified treatment groups in table KHAA.5.1 page 48 CSR KHAA (Table 25 above). In this table, it is stated that 756 patients were treated with placebo and 762 patients were treated with baricitinib in the ITT population, whilst the ITT was described to consist of all patients randomly assigned to treatment with 761 in the placebo group and 764 in the baricitinib group. The MAH has explained that numbers from Table KHAA.5.1 in the Study KHAA Day 28 CSR reflect patients based on the multiple imputation

(MI) data set for assessment of progression and odds of overall improvement. In this data set, 7 patients (5 from placebo + SOC and 2 from baricitinib + SOC) had no baseline NIAID OS score and were therefore excluded from the multiple imputation analyses because the method required imputation in strata that depended on the baseline OS. These 7 patients discontinued at the screening visit.

In the KHAA CSR, the MAH did not comment on the different factors contributing to the primary outcome measure. The table below was provided as part of the AA request. As will be detailed in the secondary efficacy results section, all-cause mortality was 5% less in the baricitinib group than in the placebo group. The MAH has provided breakdown data of clinical status at a given timepoint (Day 28) for patients progressing to (invasive) ventilation during the study. These data provide further insight in events after the first event of progression. No new concerns arise with respect to consistency of the observed results.

Furthermore, there is a substantial proportion of patients who die who never progressed to OS6 or 7, which may be counterintuitive but can be explained by the OS clinical status at baseline already being category 6 or 7, or by the fact that OS scores were recorded once a day and deterioration can be very fast in COVID-19.

N-ITT	Placebo + SoC (N=761)	Baricitinib + SoC (N=764)	Effect Size (Bari% - Pbo%)
Primary endpoint (overall): % of total population who progressed to OS6 or OS7 orOS8 (based on LOCF). N (%)	228 (30%)	206 (27%)	-3.0%
#1 Needed high flow oxygen/non-invasive ventilation (ever OS6, never OS7)	74 (9.7%)	70 (9.2%)	-0.5%
#2 Needed intubation (ever OS7)	136 (17.9%)	125 (16.4%)	-1.5%
#3 Died (OS8) (never progressed to OS6 or OS7)	18 (2.4%)	11 (1.4%)	-1%

Notably, the analysis of the primary efficacy endpoint in the population who did not receive corticosteroids at baseline revealing that 1.7% more patients progressed in the baricitinib + SOC group compared with the placebo + SOC group (28.9% vs 27.1%).

Secondary efficacy endpoints

Results for the secondary efficacy endpoint are presented in Table 26. **As Study KHAA did not meet its primary objective, no secondary endpoints met multiplicity-controlled statistical significance** and nominal p-values are presented below.

The secondary endpoint of **all-cause mortality by Day 28**, did show a clinically meaningful and nominally statistically significant (not multiplicity corrected) benefit for the overall population: a significant reduction in Day 28 all-cause mortality with 8.1% baricitinib + SOC versus 13.1% placebo + SOC group (38.2% relative reduction; HR = 0.57 [95% CI: 0.41, 0.78]; p=.002).

A greater likelihood of **improvement in NIAID OS at Day 14** was observed for the baricitinib + SOC compared to the placebo + SOC group, with a 28% greater odds at Day 14 (OR = 1.28 (95% CI, 1.05 - 1.56, nominal p=.017 [statistically significant without adjustment for multiplicity]). The effect on improvement in NIAID OS at Day 4, 7 and 10 was comparable (Day 4 OR 1.21 (95% CI 1.00-1.47), Day 7 OR 1.25 (95% CI 1.04-1.49), Day 10 OR 1.17 (95% CI 0.97-1.41)). Nominally significant improvements compared with placebo were reached for Days 4, 7, and 14.

Overall, a numerically (but not statistically significant) greater proportion of patients treated with baricitinib + SOC demonstrated at least a **1-point improvement or live discharge from hospital at Day 14** compared with placebo + SOC (75.6% vs. 72.3%, OR 1.21 (95% CI 0.95-1.55), p=0.13). The

effect on 1-point improvement or live discharge from hospital at Days 4 and 7 was comparable, while no effect was observed at Day 10 (OR 1.07; 95% CI 0.86-1.34).

A numerical (but not statistically significant) improvement was seen in the baricitinib + SOC group for **time to recovery**, with a median time to recovery of 10 days in the baricitinib + SOC group and 11 days in the placebo + SOC group (rate ratio 1.11 [95% CI 0.99 to 1.24], nominal p=0.15).

Baricitinib treated patients had a numerically higher mean number of **ventilator-free days** than patients treated with placebo (24.6 days vs 23.8 days, p=0.06).

A numerically greater proportion of patients treated with baricitinib + SOC had at least a **2-point improvement in NIAID-OS** than those treated with placebo + SOC at Days 4, 7, 10, 14, 21, and 28.

Table 26 Summary of KHAA Secondary Outcome measures by Treatment Group by Ordinal Score at Baseline ITT Population

	Overall		**Baseline OS 4 (No supplemental oxygen)**		**Baseline OS 5 (Low-flow oxygen)**		**Baseline OS 6 (Noninvasive ventilation or high-flow oxygen)**	
	PBO	**BARI**	**PBO**	**BARI**	**PBO**	**BARI**	**PBO**	**BARI**
Proportion of patients progressing to ventilation or death through Day 28[a] (Population 1: Overall population)								
N	756	762	97	89	472	490	187	183
Estimate % (95% CI)	30.5 (27.2, 33.8)	27.8 (24.6, 31.0)	9.5 (3.6, 15.4)	7.0 (1.6, 12.3)	28.3 (24.3, 32.4)	25.6 (21.7, 29.5)	46.8 (39.6, 54.0)	43.8 (36.5, 51.1)
OR (95% CI) p-value[b]	0.85 (0.67, 1.08) p=.180		0.78 (0.27, 2.22) p=.640		0.87 (0.65, 1.17) p=.352		0.85 (0.56, 1.30) p=.459	
Time to recovery								
N	761	764	97	89	472	490	187	183
Median, days (95% CI)	11.0 (10.0,12.0)	10.0 (9.0, 11.0)	9.0 (8.0, 11.0)	10.0 (8.0, 12.0)	9.0 (9.0, 10.0)	9.0 (8.0, 9.0)	0.0 17.0, 28.0)	17.0 (14.0 ,27.0)
Rate Ratio[c] (95% CI) p-value[d]	1.11 (0.99, 1.24) p=.145		1.10 (0.80, 1.50) p=.728		1.12 (0.97, 1.29) p=.193		1.11 (0.84, 1.46) p=.534	
Proportion of patients with at least 1-point improvement on NIAID OS or live discharge from hospital at Day 14[e]								
N	756	762	97	89	472	490	187	183
Estimate proportion (%) (95% CI)	72.3 (69.1,75.5)	75.6 (72.5, 78.6)	73.2 (63.6, 81.0)	73.0 (63.0, 81.2)	77.1 (73.1, 80.6)	80.1 (76.4, 83.4)	55.9 (48.7, 62.9)	55.8 (48.5, 62.8)
OR (95% CI) p-value[b]	1.21 (0.95, 1.55) p=.125		1.07 (0.56, 2.06) p=.839		1.19 (0.86, 1.63) p=.287		1.01 (0.67, 1.55) p=.945	
Odds of overall improvement on the NIAID OS evaluated at Day 14[e]								
N	756	762	97	89	472	490	187	183
OR (95% CI) p-value[f]	1.28 (1.05, 1.56) p=.017		1.36 (0.72, 2.55) p=.345		1.19 (0.92, 1.53) p=.183		1.20 (0.83, 1.72) p=.335	
All-cause mortality Day 28								

	Overall		Baseline OS 4 (No supplemental oxygen)		Baseline OS 5 (Low-flow oxygen)		Baseline OS 6 (Noninvasive ventilation or high-flow oxygen)	
	PBO	**BARI**	**PBO**	**BARI**	**PBO**	**BARI**	**PBO**	**BARI**
N	761	764	97	89	472	490	187	183
Number of deaths, n (%)	100 (13.1)	62 (8.1)	4 (4.1)	1 (1.1)	41 (8.7)	29 (5.9)	55 (29.4)	32 (17.5)
HR[g] (95% CI) p-value	0.57 (0.41, 0.78) p=.002[d]		0.24 (0, 2.18) p=.228[d]		0.72 (0.45, 1.16) p=.112[d]		0.52 (0.33, 0.80) p=.007[d]	
KM estimate, % (95% CI)	3.7 11.0, 16.9)	8.6 (6.4, 11.1)	4.2 (1.4, 12.4)	1.2 (NR, NR)	8.9 (6.4, 12.5)	6.2 (3.9, 9.1)	0.8 23.4, 39.9)	8.5 12.1, 26.0)

c. Rate ratio is the HR of the time to recovery in each treatment group estimated from the Cox model. The ratio is BARI to PBO. The ratio for the "Overall" group is the ratio from the stratified Cox model.

d p-value was calculated using the stratified log-rank test. Not multiplicity corrected.

e Overall population data are analysed using multiple imputation; OS subgroup data are analysed using LOCF.

f p-value was calculated using proportional odds model adjusted for baseline disease severity, age, region, and systemic corticosteroids used at baseline for primary study condition.

g HR is the ratio of the hazard of time to death in each treatment group estimated from the Cox model. The ratio is BARI to PBO. Hazard ratio for the "Overall" group is the HR from the stratified Cox model.

CHMP's assessment

The reduction of all-cause mortality with an effect size of 5% (although not corrected for multiplicity) is considered a clinically meaningful observation. However, its value is difficult to assess, given that the primary endpoint did not reach statistical significance.

The other secondary endpoints numerically favour baricitinib, although the effect size for the different endpoints is limited.

The MAH did not provide the sum of patients who recovered or died for the two treatment groups in this study. According to our own calculations, 90.8% recovered or died in the placebo group, and 86.2% recovered or died in the baricitinib group (by Day 29). Upon request, the MAH has explained that adding percentages of patients who recovered or died, may not provide an appropriate percentage of patients who either died or recovered by Day 28, because these patient sets are not mutually exclusive. Of patients who did not recover and did not die by Day 28, 15.3% in the placebo arm and 16.2% in the baricitinib arm are known to have recovered after Day 28 and 20.8% in the placebo arm and 14.5% in the baricitinib arm are known to have died after Day 28. For the remaining 46 placebo patients (63.9% of patients who did not recover and did not die by Day 28) and 77 baricitinib patients (69.4% of patients who did not recover and did not die by Day 28), clinical status post Day 28 is thus still unknown. This issue is not further pursued.

Strikingly, in study KHAA, patients who received baricitinib + SOC had a median time to recovery of 10 days, versus 11 days in patients who received placebo + SOC (p=0.1453). The TTR in KHAA is strikingly different from the TTR reported in study ACTT-2, where it was 7 days (baricitinib+RDV) and 8 days (PBO+RDV), this in spite of the improved standard of care at the time of KHAA. The MAH has been requested to discuss the reasons for the difference in TTR between study ACTT-2 and KHAA and refers to the difference in geographical areas where the studies have been conducted and to the amount of COVID-infections by the time the studies were conducted which may have caused the difference in TTR between the studies.

Numerically, the all-cause mortality rate is largely different between studies ACTT-2 and KHAA. Upon request the MAH commented that the KHAA mortality rate is not out of the ordinary compared to

mortality rates in e.g. the dexamethasone RECOVERY trial that supported the COVID-19 indication for dexamethasone. In addition, the differences in geographic location where the trials have been organised may have impacted mortality rate, due to regional differences in care. Interventions of starting high-flow oxygen/noninvasive ventilation or mechanical ventilation are not standardized and may differ between regions/countries. The use of corticosteroids was not considered an important factor in the observed higher mortality rate in study KHAA. Altogether, there are plausible reasons why mortality in KHAA was higher than in ACTT-2.

Ancillary analyses

Sensitivity analysis of the primary outcome measure

NA

Subgroup analyses of the primary outcome measure

- Baseline ordinal scale

The proportion of patients progressing to ventilation or death through Day 28 was reduced for all baseline ordinal scale categories; however, statistical significance was not reached (Table 25).

- Baseline corticosteroid use

Overall, 79.3% of the patients in Study KHAA received systemic corticosteroids at baseline. 91.3% of these patients were receiving dexamethasone, and 7.8% of patients were receiving methylprednisolone. The numerical improvement in favour of baricitinib compared with placebo for the primary analysis was observed (in the logistic regression analysis) whether baricitinib was taken with or without corticosteroids; the OR (95%CI) was 0.92 (0.51-1.67) for the corticosteroid use "no" group and 0.83 (0.65-1.07) for the corticosteroid use "yes" group.

- Baseline remdesivir use

Approximately 19% of patients received remdesivir at baseline (PBO + SOC 19.4% vs. BARI + SOC 18.4%). A numerical improvement in favour of baricitinib + SOC compared with placebo + SOC for the primary analysis was observed regardless of whether baricitinib was taken with or without remdesivir. The OR (95%CI) was 0.82 (0.63-1.06) for the remdesivir "no" group and 0.87 (0.49-1.51) for the remdesivir "yes" group.

CHMP' assessment

A numerical reduction in the proportion of patients progressing to ventilation or death through Day 28 was observed for all baseline ordinal scale categories.

Subgroup analyses of the primary efficacy endpoint were not presented within the results section of the KHAA CRS, and no tabulated summary or Forest plot is available. In the additional tables in the CSR, data are available for subgroups according to age, sex, weight, race, geographic region, comorbidity, pooled duration of symptoms, baseline renal function. Analysis of the primary endpoint in these subgroups indicated that a lower proportion of patients progressed in the baricitinib group, except for patients with: baseline weight <60; BMI < 25 kg/m2; race American Indian or Alaska Native; region Europe. These subgroups consisted of relatively less patients.

Although the MAH remarks that numerical improvement in favour of baricitinib compared with placebo for the primary analysis was observed whether baricitinib was taken with or without corticosteroids, this does not hold true for analysis of the primary outcome measure in Population 2 (patients requiring supp

oxygen who did not receive baseline corticosteroids). In Population 2 (N = 205), 1.7% more patients progressed in the baricitinib + SOC group compared with the placebo + SOC group (28.9% vs 27.1%). As patients with baseline OS 4 were not included in Population 2, outcome of these patients could have accounted for the divergent results. This has further been explored by a treatment by severity scale (OS 4 versus OS 5 and OS 6) interaction test, which revealed no significant difference between the subgroups. Thus the observed difference cannot be explained by the in- or exclusion of patients with baseline OS4 and the reason behind it remains unknown. This issue is not further pursued.

Subgroup analyses of the secondary outcome measures

For the secondary endpoint of **all-cause mortality by Day 28**, a reduction in mortality was observed for all *baseline severity* subgroups of baricitinib-treated patients (Table 26). This reduction was most pronounced for patients receiving noninvasive ventilation/high-flow oxygen devices at baseline (OS 6: 17.5% versus 29.4% for baricitinib + SOC versus placebo + SOC; HR = 0.52 [95% CI: 0.33, 0.80]; nominal p-value=0.007). While there seems to be a large reduction in mortality in the OS 4 subgroup (1.1% vs 4.1% for baricitinib + SOC versus placebo + SOC; HR = 0.24 [95% CI: 0 to 2.18]; nominal p-value=0.228, the vast majority (>90%) of these patients recovered by Day 28 in both treatment groups, and there was a small number of deaths overall: 1 death (1.1%) reported in the baricitinib + SOC group compared to 4 deaths (4.1%) in placebo + SOC.

A reduction in mortality was seen with baricitinib, with or without *corticosteroids* use. In the subgroup receiving background corticosteroids 82/592 patients (13.9%) died in the placebo group and 57/612 patients (9.3%) died in the baricitinib group; the relative reduction in Day-28 mortality was 31.4% (HR 0.63 [95% CI 0.45-0.89] p=0.017). In the subgroup not receiving background corticosteroids 18/164 patients (11%) died in the placebo group and 5/150 patients (3.3%) died in the baricitinib group; the relative reduction in Day-28 mortality was 69.1% (HR 0.28 [95%CI 0.10-0.77] p=0.011]).

HRs for all-cause mortality were in favour of baricitinib regardless of baseline *remdesivir* use yes/no (HR 0.81 and HR 0.51 respectively).

Lower proportions of patients died in the baricitinib group in different geographic regions, although nominal statistical significance was not reached for Europe and US, only for the rest of the world (not multiplicity corrected).

The odds of **clinical improvement at Day 14** numerically favored baricitinib + SOC compared with placebo + SOC regardless of baseline disease severity:

- OS 4: 36% greater odds in baricitinib + SOC versus placebo + SOC (OR 1.36, p=0.35)
- OS 5: 19% greater odds in baricitinib + SOC versus placebo + SOC (OR = 1.19, p=0.18)
- OS 6: 20% greater odds in baricitinib + SOC versus placebo + SOC (OR=1.20, p=0.34)

Median **time to recovery** by disease severity was as follows: In the OS 4 subgroup, patients treated with baricitinib + SOC had a longer median time to recovery than those treated with placebo + SOC (10 days vs. 9 days, respectively; 10.0% relative increase; Rate ratio = 1.10, p=0.7282). In the OS 5 subgroup, there was no difference in the median time to recovery between treatment groups (No relative reduction; Rate ratio = 1.12, p=0.193). In the OS 6 subgroup, patients treated with baricitinib + SOC had a shorter median time to recovery that those treated with placebo +SOC (17 days vs. 20 days, respectively; 15.0% relative reduction; Rate ratio = 1.11, p=0.5343). The numerical improvement in favour of baricitinib compared with placebo in the Overall group for time to recovery was consistent across baseline corticosteroid use subgroups; the rate ratio was 1.18 (0.92, 1.51) for the corticosteroid use "no" group and 1.08 (0.95, 1.23) for the corticosteroid use "yes" group.

CHMP's comment

Subgroup analysis for the secondary outcome measures of ventilator-free days and one-point improvement on the ordinal scale by Day 14 was not provided in the CSR. However, as no additional information is anticipated from these analyses, this is not further pursued.

The beneficial effect on all-cause mortality is consistent across subgroups, with the most pronounced effect in baseline OS 6.

Odds for improvement at Day 14 were numerically in favour of baricitinib across all subgroups.

A favourable effect on time to recovery was only observed for baseline OS 6, while an opposite effect was observed for baseline OS 4, and no effect was observed for baseline OS 5.

Overall, these subgroup analyses should be interpreted with caution as the study was not powered to show an effect on individual subgroups; no definitive conclusions should be drawn.

As with the ACTT-2 trial, the MAH has been requested to provide logistic regression analysis comparing the mortality rates within the 29-days follow up period, alongside the corresponding ORs and RRs. Results are consistent with Day 28 estimates of mortality provided in the CSR.

RECOVERY

As a full study report is not available, the description and assessment of this trial are based on the RECOVERY general protocol:

https://www.recoverytrial.net/files/recovery-protocol-v23-1-2022-03-15.pdf

and the published article and supplementary data on the baricitinib arm of the RECOVERY trial:

https://www.medrxiv.org/content/10.1101/2022.03.02.22271623v1.full-text

https://www.medrxiv.org/content/10.1101/2022.03.02.22271623v1.supplementary-material

The RECOVERY trial is a randomised, controlled, open-label platform trial, assessing multiple possible treatments in patients hospitalised for COVID-19. The adaptive design of the RECOVERY trial, allows for new trial arms to be added as evidence emerges that other candidate therapeutics should be evaluated. Over time, treatment arms were added and removed from the protocol, factorial randomisations were introduced, and not all treatments were available at every hospital or were deemed by the attending clinicians to be suitable for all patients. To facilitate collaboration during the COVID-19 pandemic, trial procedures were greatly streamlined; informed consent is simple, data entry is minimal and key follow-up information is recorded at a single timepoint.

CHMP's comment

Although it is acknowledged that the trial was designed during the COVID-19 pandemic to allow for a fast evaluation of different drugs that could be used in the treatment of COVID-19, its design limits the interpretability of the study results.

Methods

Study Participants

In- and exclusion criteria:

Patients aged at least 2 years admitted to hospital were eligible for the study if they had clinically suspected or laboratory confirmed SARS-CoV-2 infection and no medical history that might, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in the trial.

Patients were ineligible for the comparison of baricitinib vs. usual care if aged <2 years, eGFR <15 mL/min/1.73m^2 or on dialysis or haemofiltration, neutrophil count <0.5 × 10^9/L, had evidence of active TB infection, or were pregnant or breastfeeding.

Consent:

Written informed consent was obtained from all patients, or a legal representative if patients were too unwell or unable to provide consent.

CHMP's assessment
The in- and exclusion criteria reflect a population of patients hospitalised with COVID-19 and are considered acceptable.

Treatments

Eligible and consenting patients were randomly allocated (1:1) to either usual standard of care alone (usual care group) or usual care plus baricitinib 4 mg once daily by mouth for 10 days or until discharge if sooner (baricitinib group).

CHMP's assessment
The use of baricitinib 4 mg once daily is endorsed as this is similar to the currently registered dose.

Objectives

The primary objective is to provide reliable estimates of the effect of study treatments on all-cause mortality at 28 days after first randomisation (with subsidiary analyses of cause of death and of death at various timepoints following discharge).

The secondary objectives are to assess the effects of study treatments on duration of hospital stay; the need for (and duration of) ventilation; and, among patients not on ventilation at baseline, the composite endpoint of death or need for mechanical ventilation or ECMO

Outcomes/endpoints

The primary outcome was 28-day all-cause mortality. Secondary outcomes were time to discharge from hospital, and, among patients not on invasive mechanical ventilation at randomisation, the composite outcome of invasive mechanical ventilation (including extra-corporeal membrane oxygenation) or death.

Prespecified subsidiary clinical outcomes were use of invasive or non-invasive ventilation among patients not on any ventilation at randomisation, time to successful cessation of invasive mechanical ventilation (defined as cessation of invasive mechanical ventilation within, and survival to, 28 days), and use of renal dialysis or haemofiltration.

Prespecified safety outcomes were cause-specific mortality, major cardiac arrhythmia, thrombotic and major bleeding events, and other infections. Information on suspected serious adverse reactions was collected in an expedited fashion to comply with regulatory requirements. Outcomes were assessed at 28 days after randomisation, with further analyses specified at 6 months.

CHMP's assessment

The primary endpoint of the RECOVERY trial was D28 all-cause mortality, which is considered a robust and clinically relevant outcome measure. The secondary endpoints -discharge alive within 28 days and the composite outcome of invasive mechanical ventilation or death- provide further insight into the efficacy of baricitinib in the treatment of COVID-19.

Sample size

The larger the number randomised the more accurate the results will be, but the numbers that can be randomised will depend critically on how large the epidemic becomes. If substantial numbers are hospitalised in the participating centres then it may be possible to randomise several thousand with mild disease and a few thousand with severe disease, but realistic, appropriate sample sizes could not be estimated at the start of the trial.

Recruitment was closed when over 8150 patients had been randomised and the blinded 28-day mortality rate was 12.9% (suggesting there would be at least 1050 deaths), giving at least 90% power to detect a proportional risk reduction in the primary outcome of one-fifth at 2P=0.01. The Trial Steering Committee and all other individuals involved in the trial were masked to outcome data until after the close of recruitment.

CHMP assessment

The sample size has not been predefined and was adaptively evaluated in a blinded fashion. This approach can be accepted given the pandemic setting.

Randomisation and blinding (masking)

Baseline data were collected using a web-based case report form that included demographics, level of respiratory support, major comorbidities, suitability of the study treatment for a particular patient, and treatment availability at the study site. Data on SARS-CoV-2 vaccination status were collected from 22 December 2020.

Eligible and consenting patients were assigned in a 1:1 ratio to either usual standard of care plus baricitinib or usual standard of care alone, using web-based simple (unstratified) randomisation with allocation concealed until after randomisation. For some patients, baricitinib was unavailable at the hospital at the time of enrolment or was considered by the managing physician to be either definitely indicated or definitely contraindicated. These patients were excluded from the randomised comparison between baricitinib versus usual care.

All RECOVERY trial participants received usual standard of care. On study entry, adult participants initially underwent the *Main Randomisation*. Trial participants with clinical evidence of progressive COVID-19 (defined as oxygen saturation <92% on room air or requiring oxygen therapy, and C-reactive protein ≥75 mg/L) could be considered for the *Second Randomisation* at any time up to 21 days after the initial randomisation, and regardless of initial treatment allocation(s).

Over time, treatment arms were added and removed from the protocol, factorial randomisations were introduced (see below), and not all treatments were available at every hospital. Similarly, not all

treatments were deemed by the attending clinician to be suitable for some patients (e.g. due to comorbid conditions or concomitant medication). In any of these cases, randomisation involved fewer arms (and/or fewer factorial elements).

Main randomisation for adults

A single participant could be randomised at most to 1 arm from each of part A, B, C, D, E and F of the factorial randomisations (depending on location), and thus receive different treatments on top of usual standard of care:

- colchicine versus no additional treatment (Part A; 19 November 2020 – 5 March 2021)
- dimethyl fumarate versus no additional treatment (Part A; 15 February 2021 – ongoing)
- covalescent plasma or casivirimab+imdevimab versus no additional treatment (Part B; 14 May 2020 – 21 May 2021)
- aspirin versus no additional treatment (Part C; 1 November 2020 – 21 March 2021)
- baricitinib versus no additional treatment (Part D; 26 January 2021 – 29 November 2021)
- high dose dexamethasone versus no additional treatment (Part E; 25 May 2021 – ongoing)
- empagliflozin versus no additional treatment (Part F; 25 May 2021 – ongoing)

Second randomization

Further, participants could be randomized to receiving tocilizumab or no additional treatment on top of those treatments above, in a second randomization.

- tocilizumab versus no additional treatment (second randomization; 14 April 2020 – 24 January 2021)

Participants and local study staff were not masked to the allocated treatment. The Trial Steering Committee, investigators, and all other individuals involved in the trial were masked to outcome data during the trial.

CHMP's comment

All RECOVERY trial participants received usual standard of care. Upon study entry, adult participants initially underwent Main Randomisation in which a single participant could be randomised to receive different treatments on top of usual standard of care. Trial participants with clinical evidence of progressive COVID-19 could be considered for the Second Randomisation to be allocated to receive additional tocilizumab or not.

Consenting patients eligible for baricitinib treatment, were assigned in a 1:1 ratio to either usual SoC plus baricitinib 4 mg once daily, or usual SoC alone.

Randomization was not stratified which may have impacted the study results. The MAH is requested to discuss the impact of the lack of stratification for site and baseline disease severity on the study results.

The open label design may lead to underestimation of the effect of SoC alone. However, the primary endpoint of D28 mortality is considered sufficiently robust to outweigh this limitation.

Statistical methods

An online follow-up form was completed by site staff when patients were discharged, had died, or at 28 days after randomisation, whichever occurred first. Information was recorded on adherence to allocated trial treatment, receipt of other COVID-19 treatments, duration of admission, receipt of respiratory or renal support, new cardiac arrhythmia, thrombosis, clinically significant bleeding, non-COVID infection, and vital status (including cause of death). In addition, routinely collected healthcare and registry data were obtained, including information on vital status at day 28 (with date and cause of death); discharge from hospital; and receipt of respiratory support or renal replacement therapy. The main analyses described above will be unadjusted for baseline characteristics. However, if there are any important imbalances between the randomised groups in key baseline prespecified subgroups or allocation in the orthogonal components of the main randomisation, where applicable, emphasis will be placed on analyses that are adjusted for the relevant baseline characteristic(s). This will be done using Cox regression for the estimation of adjusted hazard ratios and a log-binomial regression model for the estimation of adjusted risk ratios.

For the primary outcome of 28-day mortality, the hazard ratio from an age-adjusted Cox model was used to estimate the mortality rate ratio. We constructed Kaplan-Meier survival curves to display cumulative mortality over the 28-day period. We used the same method to analyse time to hospital discharge and successful cessation of invasive mechanical ventilation, with patients who died in hospital right-censored on day 29. Median time to discharge was derived from Kaplan-Meier estimates. For the pre-specified composite secondary outcome of progression to invasive mechanical ventilation or death within 28 days (among those not receiving invasive mechanical ventilation at randomisation), and the subsidiary clinical outcomes of receipt of ventilation and use of haemodialysis or haemofiltration, the precise dates were not available and so a log-binomial regression model was used to estimate the age-adjusted risk ratio. Estimates of rate and risk ratios (both denoted RR) are shown with 95% confidence intervals.

Prespecified analyses of the primary outcome were done in subgroups defined by six characteristics at the time of randomisation (age, sex, ethnicity, days since symptom onset, level of respiratory support, and use of corticosteroids) with tests of heterogeneity or trend, as appropriate. The full database is held by the study team which collected the data from study sites and performed the analyses at the Nuffield Department of Population Health, University of Oxford (Oxford, UK).

The independent Data Monitoring Committee reviewed unblinded analyses of the study data and any other information considered relevant to the trial at intervals of around 2 to 4 weeks (depending on speed of enrolment) and was charged with determining if, in their view, the randomised comparisons in the study provided evidence on mortality that was strong enough (with a range of uncertainty around the results that was narrow enough) to affect national and global treatment strategies.

As stated in the protocol, appropriate sample sizes could not be estimated when the trial was being planned. On the advice of the Trial Steering Committee, recruitment to this comparison was closed on 29 December 2021 when over 8150 patients had been randomised and the blinded 28-day mortality rate was 12.9% (suggesting there would be at least 1050 deaths), giving at least 90% power to detect a proportional risk reduction in the primary outcome of one-fifth at 2P=0.01. The Trial Steering Committee and all other individuals involved in the trial were masked to outcome data until after the close of recruitment.

CHMP's assessment

In the SAP, it is mentioned that "The main analyses described above will be unadjusted for baseline characteristics. However, if there are any important imbalances between the randomised groups in key baseline prespecified subgroups or allocation in the orthogonal components of the main randomisation,

where applicable, emphasis will be placed on analyses that are adjusted for the relevant baseline characteristic(s). This will be done using Cox regression for the estimation of adjusted hazard ratios and a log-binomial regression model for the estimation of adjusted risk ratios."

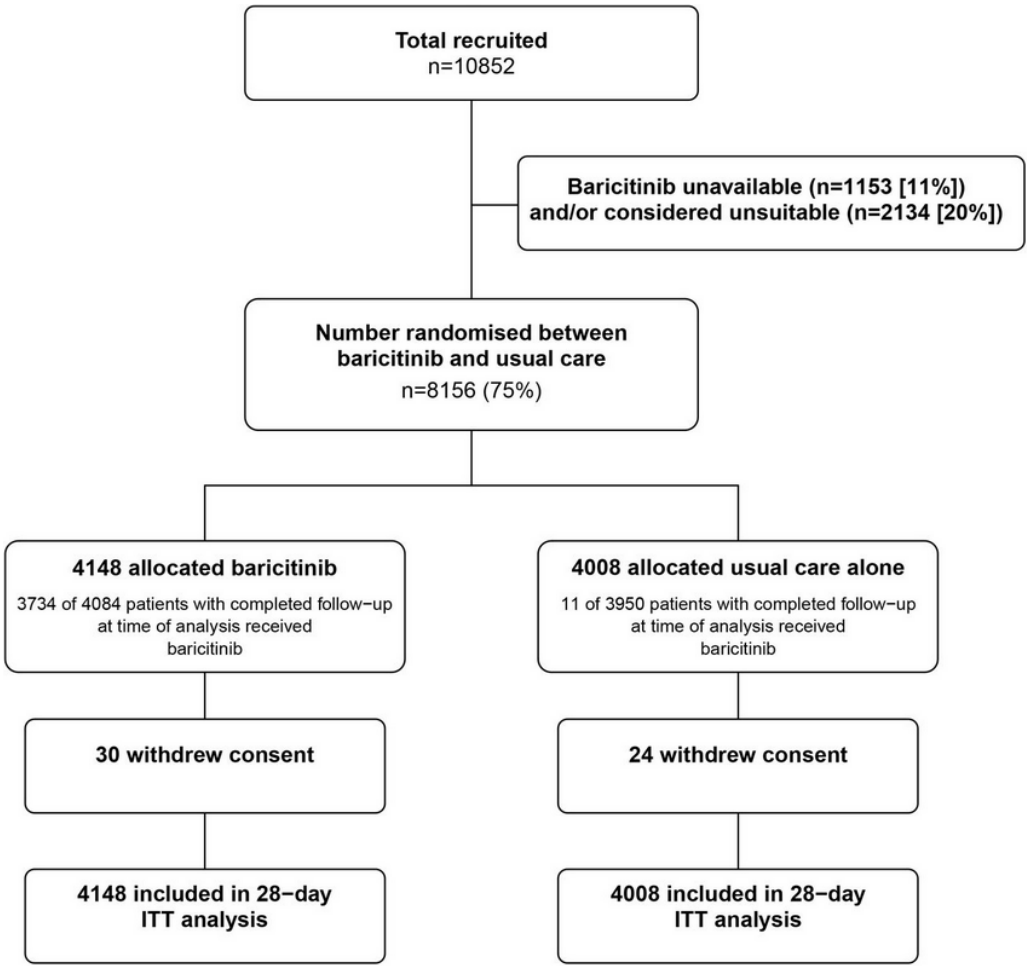
With respect to prospectively defined analysis goals, the definition of "*important imbalances"* is lacking. It is also not clear what is meant by "*emphasis will be placed".* See also discussion in Section "Outcomes and Estimation".

Further, the that the intended level of significance at which the primary analysis is to be performed is not entirely clear. In the SAP, it is mentioned that: "Evaluation of the primary trial (main randomisation) and secondary randomisation will be conducted independently, and no adjustment be made for these. Formal adjustment will not be made for multiple treatment comparisons, the testing of secondary and subsidiary outcomes, or subgroup analyses (with one exception; see Appendix A). However, due allowance for multiple testing will be made in the interpretation of the results: the larger the number of events on which a comparison is based and the more extreme the P-value after any allowance has been made for the nature of the particular comparison (i.e. primary or secondary; pre-specified or exploratory), the more reliable the comparison and, hence, the more definite any finding will be considered. 95% confidence intervals will be presented for the main comparisons." Even though the 95% CI could be read as implying a prospectively defined 5% two-sided significance level, it refers to all ("main") comparisons, which makes interpretation less straightforward. It is furthermore implied that the level of evidence will depend on the amount of information in which a comparison will be based. Furthermore, at the timing of recruitment closing, and in a blinded fashion, a two-sided significance level of 0.01 is introduced, at which a 90% power was calculated. Given the relatively large sample size, this level of significance would be considered appropriate.

Results

Participant flow

Figure 9 Participant flow - RECOVERY



Between 2 February 2021 and 29 December 2021, 8156 (75%) of 10852 patients enrolled into the RECOVERY trial at one of the 169 participating sites were eligible to be randomly allocated to baricitinib (i.e. the treatment was available in the hospital at the time and the attending clinician was of the opinion that the patient had no known indication for or contraindication to it). 4148 patients were randomly allocated to baricitinib and 4008 were randomly allocated to usual care. The follow-up form was completed for 4084 (98%) patients in the baricitinib group and 3950 (99%) patients in the usual care group.

CHMP's assessment

20% of patients recruited were not randomised. In 11% this was due to unavailability of baricitinib at the respective study site. During the assessment, the MAH was requested to present the reasons for baricitinib unsuitable for the remaining 9% of patients and to discuss the difference in terms of baseline characteristics between the 20% who were not randomised and the patients randomised. The MAH indicated that the Recovery trial did not collect reasons why all individual participants were considered unsuitable, as investigators were allowed to indicate any individual as unsuitable, even if they did not meet the protocol-specified exclusion criteria. With regard to the baseline characteristics, no major

discrepancies could be observed between patients not randomised (n=2134) and patients randomised (n=8156).

Strikingly, 10% of patients allocated to baricitinib did not receive baricitinib (414 out of 4148). Upon request, the MAH indicated that the reason for these patients not receiving their allocated treatment is not known.

Recruitment

Recruitment for baricitinib started 26 January 2021 and closed on 29 December 2021. As stated in the protocol, appropriate sample sizes could not be estimated when the trial was being planned. On the advice of the Trial Steering Committee, recruitment to this comparison was closed on 29 December 2021 when over 8150 patients had been randomised and the blinded 28-day mortality rate was 12.9% (suggesting there would be at least 1050 deaths), giving at least 90% power to detect a proportional risk reduction in the primary outcome of one-fifth at 2P=0.01. The Trial Steering Committee and all other individuals involved in the trial were masked to outcome data until after the close of recruitment.

Conduct of the study

Protocol versions and brief description of changes are listed in the table below.

13.0	26-Jan-2021	Addition of baricitinib and anakinra (and change to allocation ratio in second randomisation for children); addition of pregnancy test for women of child-bearing potential (and change to colchicine eligibility); removal of tocilizumab for adults; removal of convalescent plasma and additional assessment of antibody-based therapy; addition of dexamethasone as substitute if methylprednisolone unavailable
14.0	15-Feb-2021	Addition of Early Phase Assessments; the inclusion of dimethyl fumarate for initial early phase assessment; restriction of main randomisation part B to children with COVID-19 pneumonia; modification of baricitinib and tocilizumab co-administration guidance
15.0	12-Apr-2021	Removal of aspirin and colchicine; addition of infliximab and high-dose corticosteroids (ex-UK only)
15.1 [not submitted in UK]	18-May-2021	Addition of South Africa
16.0	05-Jul-2021	Removal of REGN-COV2 and main randomisation part B Removal of infliximab from main randomisation part E (and associated endemic infection monitoring section) Addition of empagliflozin as main randomisation part F and metabolic outcomes Addition of India, Sri Lanka and Pakistan
V16.1	08-Jul-2021	Clarification of design in introduction
V17.0	06-Aug-2021	Addition of additional exclusion criteria and safety monitoring for empagliflozin arm Removal of corticosteroids and intravenous immunoglobulin in main randomisation part A (for children)
V17.1	10-Aug-2021	Clarification of design for children
V18.0	13-Oct-2021	Update to consent section Change in primary outcome and sample size for DMF comparison Clarification of eligibility for PIMS-TS randomisation Removal of 3 month follow-up form for non-UK countries
V18.1	24-Oct-2021	Clarification of witnesses for consent of children

CHMP's assessment

The adaptive study design allows for a timely evaluation of various treatment options. However, the results of this complex adaptive platform study can be influenced by interim analyses and protocol amendments. Given the pandemic setting this can be understandable as long as no data driven decisions have been made with a potentially significant impact on the primary efficacy outcome for baricitinib. The protocol versions with brief descriptions of the main changes do not lead to concerns.

Baseline data

66% of participants were male; 35% of participants were female. The mean age of study participants in this comparison was 58.1 years (SD 15.5) with a chance imbalance whereby patients randomly allocated to baricitinib were, on average, 0.8 years older than those allocated usual care group. At randomisation, 7771 (95%) patients were receiving corticosteroids, 1872 (23%) were receiving tocilizumab (with planned use within the next 24 hours recorded for a further 756 [9%]). About two-thirds were receiving simple oxygen and one quarter were receiving non-invasive ventilation, with small numbers receiving invasive mechanical ventilation or no respiratory support at all. 3420 (42%) patients had received at least one dose of a SARS-CoV-2 vaccine. See table below.

Table 27 Baseline characteristics by treatment allocation

	Treatment allocation	
	Baricitinib (n=4148)	**Usual care (n=4008)**
Age, years	58.5 (15.4)	57.7 (15.5)
<70	3142 (76%)	3086 (77%)
≥70 to <80	665 (16%)	655 (16%)
≥80	341 (8%)	267 (7%)
Sex		
Male	2740 (66%)	2638 (66%)
Female	1408 (34%)	1370 (34%)
Ethnicity		
White	3192 (77%)	3104 (77%)
Black, Asian, and minority ethnic	457 (11%)	455 (11%)
Unknown	499 (12%)	449 (11%)
Number of days since symptom onset	9 (6-12)	9 (6-11)
Number of days since admission to hospital	1 (1-3)	1 (1-3)
Respiratory support received		
None	228 (5%)	237 (6%)
Simple oxygen	2770 (67%)	2743 (68%)
Non invasive ventilation	1016 (24%)	911 (23%)
Invasive mechanical ventilation	134 (3%)	117 (3%)
Laboratory measurements		
CRP, mg/L	84 (42-146)	87 (44-143)
Creatinine, umol/L	76 (63-93)	77 (63-94)
Previous diseases		
Diabetes	961 (23%)	941 (23%)
Heart disease	782 (19%)	706 (18%)
Chronic lung disease	882 (21%)	783 (20%)
Tuberculosis	0 (0%)	0 (0%)
HIV	13 (<1%)	9 (<1%)
Severe liver disease *	33 (<1%)	33 (<1%)
Severe kidney impairment †	101 (2%)	79 (2%)
Any of the above	1957 (47%)	1834 (46%)
SARS-CoV-2 PCR test result		
Positive	3750 (90%)	3655 (91%)
Negative	50 (1%)	39 (<1%)
Unknown	348 (8%)	314 (8%)
Received a COVID-19 vaccine	1755 (42%)	1665 (42%)
Use of other treatments		
Corticosteroids	3962 (96%)	3809 (95%)
Remdesivir	878 (21%)	789 (20%)
Tocilizumab	951 (23%)	921 (23%)
Plan to use tocilizumab within the next 24 hours	391 (9%)	365 (9%)
Other randomly assigned treatments		
Colchicine	401 (10%)	401 (10%)
Aspirin	462 (11%)	453 (11%)
Casirivimab-imdevimab	440 (11%)	449 (11%)

Data are mean (SD), n (%), or median (IQR). 33 children and no pregnant women were randomised. 2 post-partum women were randomised to baricitinib *Defined as requiring ongoing specialist care. †Defined as estimated glomerular filtration rate <30 mL/min/1.73 m²

CHMP´s comment

The baseline disease characteristics of the evaluated ITT population were very well balanced across treatment arms, with most subjects being white (77%), of male gender (66%), 9 days since symptom onset and 1 day since hospital admission. Mean age in the baricitinib group was 58.5 years [SD 15.4] and mean age in the SoC group was 57.7 years [SD 15.5]. The amount of patients receiving respiratory support and the type of respiratory support were balanced across treatment arms. 96% of patients in the baricitinib group and 95% of patients in the SoC group received concomitant corticosteroid treatment and in both groups 23% received concomitant treatment with tocilizumab.

Numbers analysed

4148 patients were randomly allocated to baricitinib and 4008 were randomly allocated to usual care. The follow-up form was completed for 4084 (98%) patients in the baricitinib group and 3950 (99%) patients in the usual care group.

Outcomes and estimation

Primary and secondary outcome data are known for >99% of randomly assigned patients.

Allocation to baricitinib was associated with a significant reduction in the primary outcome of 28-day mortality compared with usual care alone: 513 (12%) of 4148 patients in the baricitinib group died vs 546 (14%) of 4008 patients in the usual care group (age-adjusted rate ratio 0·87; 95% CI 0·77–0·98; p=0·026). Similar proportional risk reductions were seen in sensitivity analyses adjusted for all pre-specified subgroups and without adjustment for the 0.8 year age-imbalance between randomised groups, and when restricted to participants with a positive SARS-CoV-2 PCR test (age adjusted RR 0.90, 95% CI 0.79-1.02).

Discharge alive within 28 days was more common among those allocated to baricitinib compared with usual care (80% vs. 78%; age-adjusted rate ratio 1·10, 95% CI 1·04 to 1·15; median 8 days [IQR 5 to 17] vs. 8 days [IQR 5 to 20]) (please refer to the table below). Among patients not on invasive mechanical ventilation at baseline, allocation to baricitinib was associated with a lower risk of progressing to the composite secondary outcome of invasive mechanical ventilation or death (16% vs. 17%, age-adjusted risk ratio 0·90, 95% CI 0·81 to 0·99) (please refer to the table below).

Table 28 RECOVERY Primary and secondary outcome measures

	Treatment allocation			
	Baricitinib (n=4148)	Usual care (n=4008)	RR (95% CI)	p-value
Primary outcome				
28-day mortality	513 (12%)	546 (14%)	0.87 (0.77-0.98)	0.026
Secondary outcomes				
Median (IQR) time to being discharged alive, days	8 (5 to 17)	8 (5 to 20)		
Discharged from hospital within 28 days	3337 (80%)	3137 (78%)	1.10 (1.04-1.15)	<0.001
Receipt of invasive mechanical ventilation or death*	631/4014 (16%)	670/3891 (17%)	0.90 (0.81-0.99)	0.026
Invasive mechanical ventilation	283/4014 (7%)	322/3891 (8%)	0.87 (0.74-1.01)	0.06
Death	475/4014 (12%)	502/3891 (13%)	0.89 (0.80-1.00)	0.049
Subsidiary clinical outcomes				
Receipt of ventilation †	595/2998 (20%)	637/2980 (21%)	0.93 (0.84-1.03)	0.17
Non-invasive ventilation	585/2998 (20%)	623/2980 (21%)	0.94 (0.85-1.04)	0.20
Invasive mechanical ventilation	131/2998 (4%)	148/2980 (5%)	0.90 (0.71-1.13)	0.35
Successful cessation of invasive mechanical ventilation ‡	61/134 (46%)	43/117 (37%)	1.28 (0.86-1.89)	0.22
Use of haemodialysis or haemofiltration §	85/4140 (2%)	109/4003 (3%)	0.77 (0.58-1.01)	0.06

Data are n (%) or n/N (%), unless otherwise indicated. RR=rate ratio for the outcomes of 28-day mortality, hospital discharge and successful cessation of invasive mechanical ventilation, and risk ratio for other outcomes. CI=confidence interval. Estimates of the RR and its 95% CI are adjusted for age in three categories (<70 years, 70-79 years, and 80 years or older). * Analyses exclude those on invasive mechanical ventilation at randomisation. † Analyses exclude those on any form of ventilation at randomisation. ‡ Analyses restricted to those on invasive mechanical ventilation at randomisation. § Analyses exclude those on haemodialysis or haemofiltration at randomisation.

CHMP's assessment

Per study protocol, the primary analysis was performed in the ITT population and thus included 4148 patients in the baricitinib arm and 4008 patients in the SoC arm, of whom 513 (12.4%) and 546 (13.6%) of patients had died by Day 28. Although with a limited effect size (1.2%), a reduction in 28-day mortality was observed in patients treated with baricitinib. Notably, the difference between the groups only became significant after adjustment for age or after adjustment for all prespecified co-variates (age, sex, race, respiratory support, days since symptom onset). Please refer to the table below, obtained from the supplementary material with the medRxiv publication of the study results (Baricitinib in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial and updated meta-analysis. RECOVERY Collaborative Group (medRxiv preprint doi:

https://doi.org/10.1101/2022.03.02.22271623; version posted March 3, 2022)).

Webtable 3: Impact of adjusting for the 0.8-year age imbalance between randomised arms (and of further adjusting for all other predefined subgroups) on the estimated effect of allocation to baracitinib on 28-day mortality

	Treatment allocation			
	Baricitinib (n=4148)	Usual care (n=4008)	RR (95% CI)	p-value
Main age-adjusted analysis*	513 (12.4%)	546 (13.6%)	0.87 (0.77-0.98)	0.026
Fully-adjusted †	513 (12.4%)	546 (13.6%)	0.85 (0.75-0.96)	0.008
No adjustments ‡	513 (12.4%)	546 (13.6%)	0.90 (0.80-1.02)	0.09

* Main analysis shown in Figures 2 and 3, in which the 28-day age-adjusted (ie, conditional) mortality rate ratio is estimated by the hazard ratio from a Cox regression analysis adjusted for age in three categories (<70 years, 70-79 years, and 80 years or older).

† Further adjusted for other pre-defined subgroups shown in Figure 3.

‡ Analysis without adjustment for the 0.8-year age-imbalance between the randomized groups. With this method the 'one-step' method is used to estimate the average unadjusted (ie, marginal) mortality rate ratio from the log-rank 'observed minus expected' statistic (O –E) and its variance (V), through the formula exp([O – E] ÷ V). Its 95% CI is then given by exp([O – E] ÷ V ± 1.96 ÷ sqrt V).

The MAH presents the age-adjusted RR as the primary analysis supporting efficacy. However, the prospective nature of this analysis is not justified. In the statistical analysis plan for the RECOVERY trial, it is mentioned that *"The main analyses described above will be unadjusted for baseline characteristics. However, if there are any important imbalances between the randomised groups in key baseline prespecified subgroups or allocation in the orthogonal components of the main randomisation, where applicable, emphasis will be placed on analyses that are adjusted for the relevant baseline characteristic(s). This will be done using Cox regression for the estimation of adjusted hazard ratios and a log-binomial regression model for the estimation of adjusted risk ratios."* Neither "any important imbalances" nor "emphasis will be placed" have been further specified. While from a clinical point of view age as a prognostic factor for COVID-19 is acknowledged, there was only a marginal difference in mean age of 0.8 years with standard deviations largely overlapping (mean age baricitinib group 58.5 years (SD 15.4) and mean age SoC group 57.7 years (SD 15.5)). Thus, the choice of age as the controlling variable on which the primary analysis is based is not justified. Furthermore, the "imbalance" of 0.8 years difference in mean age between groups is not reflected in the categorical variable describing different age categories, in which the imbalance is of no larger magnitude than any other prognostic variables for which corrected analyses were thought to be of relevance. However, the categorical age variable is chosen as the one used for correction in the main analysis. Given the lack of clearly pre-specified conditions for an adjusted analysis and the discrepancy between the variable on which "imbalance" is observed (continuous age) and the variable on which the corrected estimate is based (age categories), the age-adjusted RR is not acceptable as a primary efficacy measure. Thus the unadjusted analysis is considered the main analysis and its outcome does not reach statistical significance.

The uncertainty surrounding the conclusion of efficacy of baricitinib is further perplexed by the significance level to be employed in the main analysis (see above). In addition to the concerns raised with respect to the adjusted analysis, it should be noted that the significance level of 0.01, implied by the decision to stop recruitment, is not reached, even with the age-adjusted analysis.

Strikingly, 10% of patients allocated to baricitinib did not receive baricitinib (414 out of 4148). Upon request, the MAH indicated that the reason for these patients not receiving their allocated treatment is not known. It turned out that mortality in this subgroup was above 20% (data not shown here). The

MAH is requested to present the baseline characteristics for patients not receiving their assigned treatment with baricitinib as compared to baseline characteristics of patients wo did receive their treatment with baricitinib and to discuss the reasons for the apparently high mortality rate in the group of patients that did not receive baricitinib treatment while assigned. Furthermore, it turned out that the data presented by the MAH are not the final RECOVERY data. Given the uncertainties surrounding the primary outcome measure, the final decision on this procedure should be based on all available data and hence the MAH should provide all analyses based on the updated datacut. (OC)

For the secondary endpoints, only age adjusted rate ratios have been provided, thus the results should be interpreted with caution. Patients treated with baricitinib had a significantly higher chance to be discharged alive within 28 days compared with usual care (80% vs. 78%; age-adjusted rate ratio 1·10, 95% CI 1·04 to 1·15; median 8 days [IQR 5 to 17] vs. 8 days [IQR 5 to 20]) and a lower risk of progressing to the composite secondary outcome of invasive mechanical ventilation or death (16% vs. 17%, age-adjusted risk ratio 0·90, 95% CI 0·81 to 0·99).

Although a small effect in favour of baricitinib can be observed across the prespecified subsidiary clinical outcome measures, statistical significance was not reached.

Ancillary analyses

The proportional effect of baricitinib on mortality was consistent across all pre-specified subgroups, including by level of respiratory support received (test for trend p=0.33), use of dexamethasone at randomisation (test for heterogeneity p=0.41) and, in exploratory analyses, by baseline CRP level (test for trend p=0.93) or by use of tocilizumab or remdesivir at baseline (tests for heterogeneity p=0.53 and p=0.12, respectively).

There was no evidence that the effect of baricitinib on mortality varied depending on concurrent randomised allocation to colchicine, aspirin or casirivimab+imdevimab (all interaction p-values >0.32).

Table 29 Effect of allocation to baricitinib on 28–day mortality by pre-specified baseline characteristics

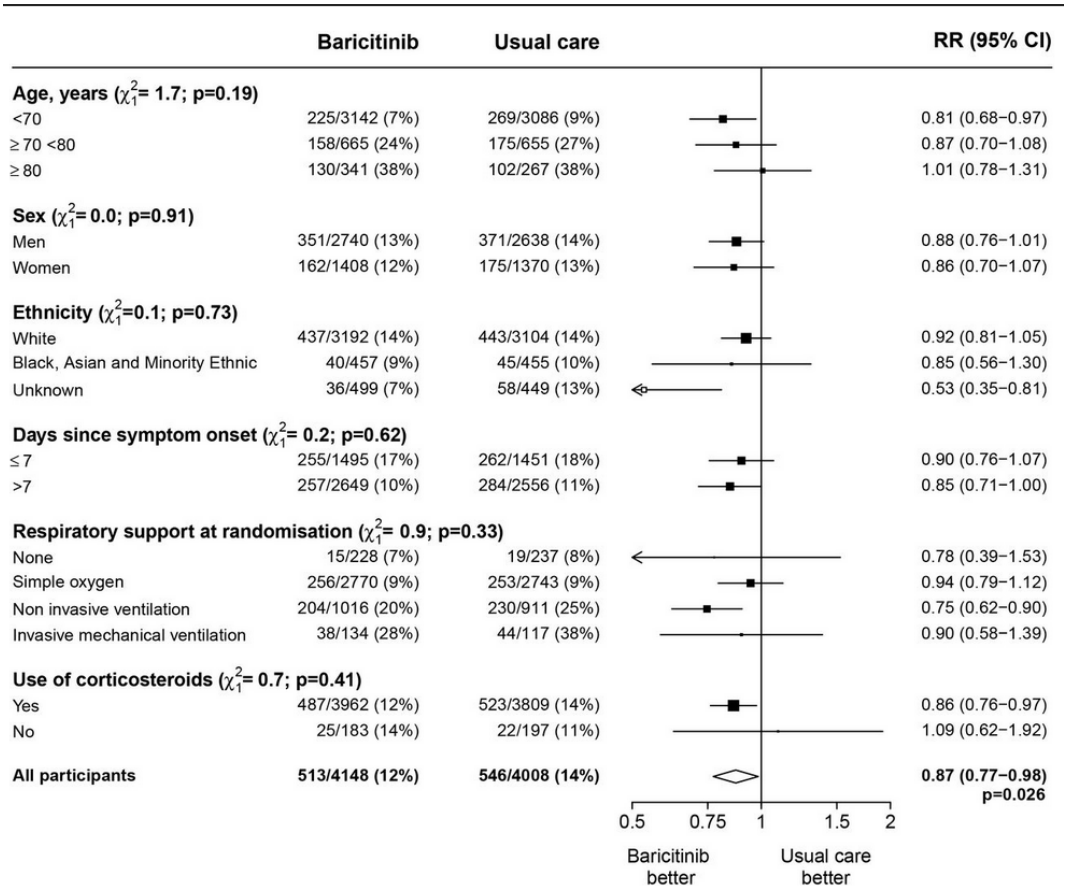
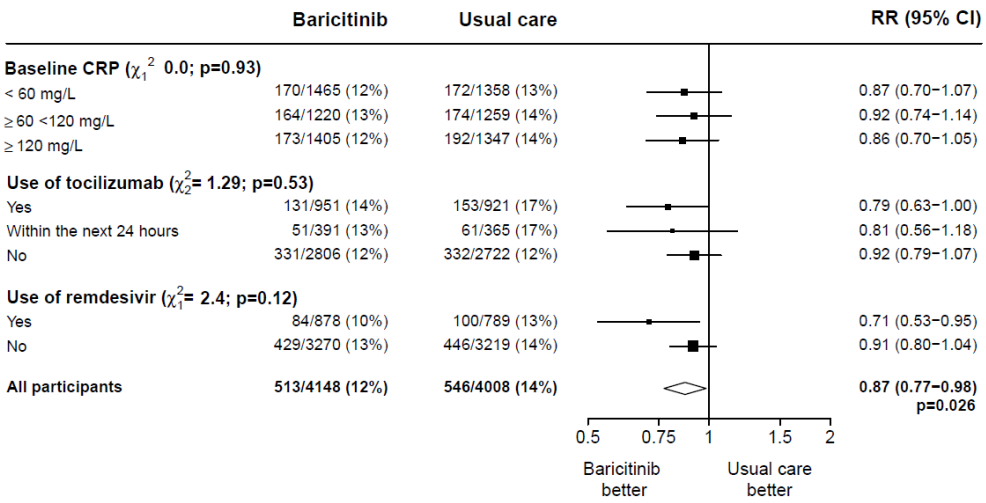


Table 30 Effect of allocation to baricitinib on 28-day mortality by subgroup defined retrospectively



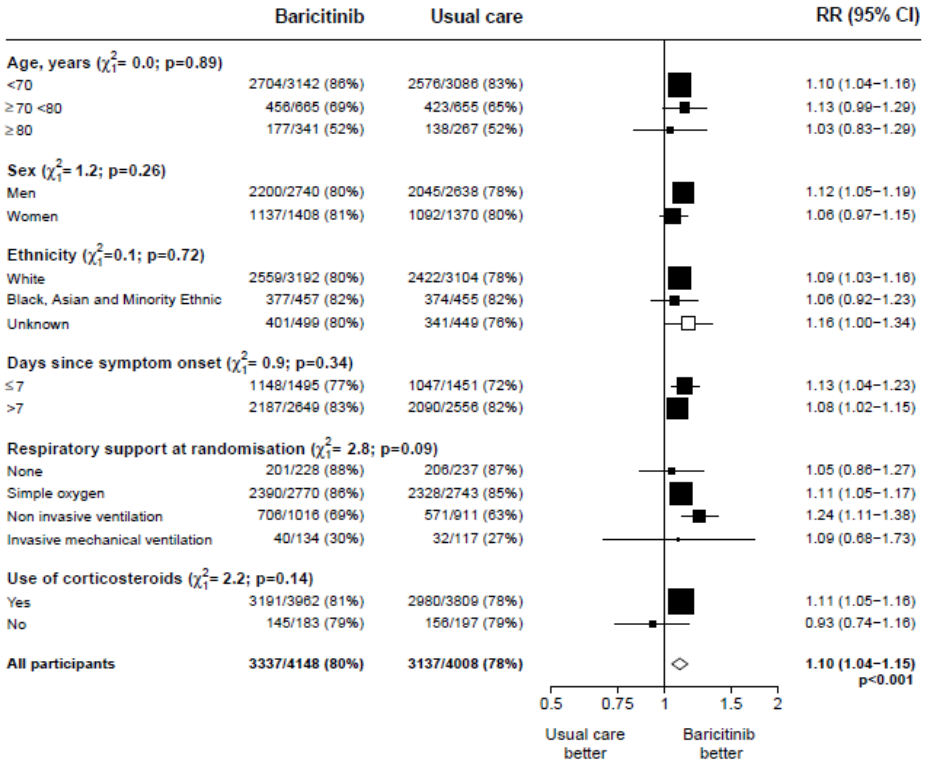
Subgroup–specific rate ratio estimates are represented by squares (with areas of the squares proportional to the amount of statistical information) and the lines through them correspond to 95% CIs. Subgroup–specific estimates exclude those with missing data, but these patients are included in the overall summary diamond. RR=age adjusted rate ratio.

CHMP assessment

The proportional effect of baricitinib on mortality was consistent across pre-specified subgroups, except for patients aged older than 80 years in whom no benefit in D28 mortality was observed (see also section on efficacy in special populations) and for the very small group of patients who did not receive corticosteroids at baseline in whom there seems to be a small opposite effect, though with large uncertainty. The effect of baricitinib was also comparable across posthoc defined subgroups categorized by CRP, tocilizumab use and remdesivir use.

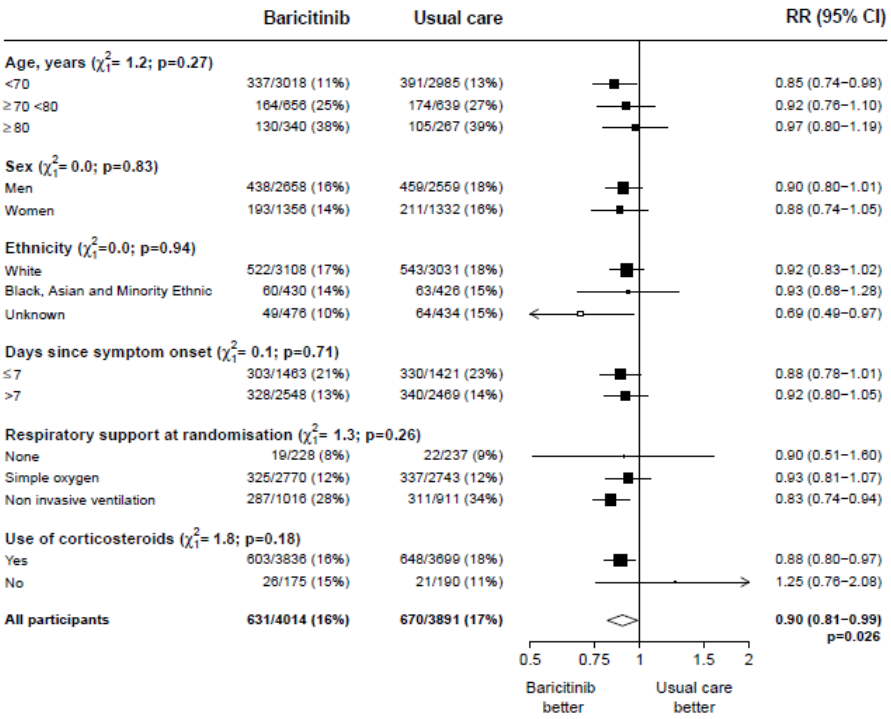
The proportional effects of baricitinib versus usual care on secondary outcomes were also similar across all pre-specified subgroups.

Table 31 Effect of allocation to baricitinib on hospital discharge by pre-specified baseline characteristics



Subgroup–specific rate ratio estimates are represented by squares (with areas of the squares proportional to the amount of statistical information) and the lines through them correspond to 95% CIs. The days since onset and use of corticosteroids subgroups exclude patients with missing data, but these patients are included in the overall summary diamond.
RR=age adjusted rate ratio.

Table 32 Effect of allocation to baricitinib on on invasive mechanical ventilation or death in those not on invasive mechanical ventialation at randomisation by pre-specified baseline characteristics



Subgroup–specific rate ratio estimates are represented by squares (with areas of the squares proportional to the amount of statistical information) and the lines through them correspond to 95% CIs. The days since onset and use of corticosteroids subgroups exclude patients with missing data, but these patients are included in the overall summary diamond.
RR=age adjusted rate ratio.

CHMP's assessment
The proportional effects of baricitinib versus usual care on secondary outcomes were also similar across pre-specified subgroups, except the small group of patients without corticosteroids in whom the effect on secondary outcome measures seems to go in opposite direction though with large uncertainty.

2.5.3. Summary of main *study(ies)*

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy and the benefit-risk assessment (see later sections).

*Table 33 Summary of Efficacy for trial **ACTT-2***

Title: A Multicenter, Adaptive, Randomized Blinded Controlled Study of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19+ in Hospitalized Adults, ACTT-2: Baricitinib/Remdesivir vs Remdesivir		
Study identifier	ACTT-2 (part of ACTT, EudraCT Number: 2020-001052-18)	
Design	Multicenter, randomized, double-blind, placebo-controlled trial	
	Duration of main phase: 29 days	
Hypothesis	Superiority	
Treatments groups	Baricitinib + remdesivir	Baricitinib tablets (4mg – two 2mg tablets – PO QDay x 14 days) + Remdesivir IV (200mg IV loading dose Day 1; 100mg IV Q Day for 10 days total)

	Placebo + remdesivir		Placebo tablets (two tablets PO QDay x 14 days) + Remdesivir IV (200mg IV loading dose Day 1; 100mg IV Q Day for 10 days total)
Endpoints and definitions	Primary endpoint	Time to recovery (days)	Difference between treatment groups in time to recovery, where recovery is defined as clinical status in states 1, 2, or 3 of the 8-point ordinal scale, censored at Day 29 (stratified log-rank test)
	Secondary endpoints	Proportion of patients progressing to ventilation or death (%)	Difference between treatment groups in proportion of patients who died or require noninvasive ventilation/high-flow oxygen or invasive mechanical ventilation (including ECMO) by Day 29 (logistic regression)
		Overall improvement of NIAID OS at Day 15 (OR)	Difference between treatment groups in overall improvement on the NIAID-OS evaluated at Day 15 (proportional odds model)
Database lock	10 September 2020		
Results and Analysis			
Analysis description			
Analysis population and time point description	As treated population (all patients randomized who received at least one dose of the study drugs), Day 1 to Day 29 (unless indicated to be otherwise)		

Endpoint, statistics and estimate variability	Treatment group	Baricitinib + remdesivir	Placebo + remdesivir	Rate ratio (95% CI), p-value
	Number of subjects, n	507	509	
	Primary Analysis			
	Time to recovery *Median, days (95% CI)*	7.0 (6.0, 8.0)	8.0 (7.0, 9.0)	1.16 (1.01, 1.33) P=0.03
	Secondary Analysis			
	Proportion of patients progressing to ventilation or death through Day 29 *Estimate % (95% CI)*	23 (19, 27)	29 (25, 33)	0.73 (0.55, 0.97) p=0.03 *(nominal p-value, not corrected for multiplicity)*
	Odds of overall improvement on the NIAID OS evaluated at Day 15 *Distribution across ordinal scale at Day 15*	-	-	1.26 (1.01, 1.58) p=0.04
	All-cause mortality by Day 29 *Number of deaths, n (%)*	23 (4.5)	37 (7.3)	0.63 (0.37, 1.05) p=0.08

*Table 34 Summary of Efficacy for trial **KHAA/COV-BARRIER***

Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Phase 3 Study of Baricitinib in Patients with COVID-19 Infection	
Study identifier	I4V-MC-KHAA (EudraCT Number: 2020-001517-21)
Design	Multicenter, randomized, double-blind, placebo-controlled, parallel-group trial

	Duration of main phase:		28 Days (Follow-up until Day 60)
Hypothesis	Superiority		
Treatments groups	Baricitinib + SOC		Baricitinib 4 mg QD, administered as two 2-mg tablets. Duration of treatment was up to 14 days, or up to the day of hospital discharge, whichever occurred first.
	Placebo + SOC		Placebo QD, administered as 2 placebo tablets. Duration of treatment was up to 14 days, or up to the day of hospital discharge, whichever occurred first.
Endpoints and definitions	Primary endpoint	Proportion of patients who die or require non-invasive ventilation/high-flow oxygen or invasive mechanical ventilation (including ECMO) by Day 28	Difference in the proportion of patients progressing to ventilation or death through Day 28. The primary endpoint reflects any event of progression or death. This endpoint does not differentiate outcomes subsequent to the progression. Endpoint analysed in: • Population 1 – all randomized patients • Population 2 – patients who, at baseline, require oxygen supplementation and are not receiving corticosteroids for the primary study condition. (logistic regression analysis)
	Secondary endpoints	Time to recovery by Day 1 to 28 (median days)	Difference between treatment groups in time to recovery, where recovery is defined as clinical status in states 1, 2, or 3 of the 8-point ordinal scale
		Overall improvement of NIAID OS at Day 14 (OR)	Difference between treatment groups in overall improvement on the NIAID-OS evaluated at Day 14
		All-cause mortality by Day 28 (%)	Difference between treatment groups in all-cause mortality (Day 1-Day 28) (stratified log rank test)
Database lock	23 March 2021		

Results and Analysis

Analysis description

Analysis population and time point description	ITT population			
Endpoint, statistics and estimate variability	Treatment group	Baricitinib + remdesivir	Placebo + remdesivir	Rate ratio (95% CI), p-value
	Number of subjects, n	764	761	
	Primary Analysis			
	Proportion of patients progressin g to ventilation or death through Day 2 *Estimate % (95% CI)*	27.8 (24.6, 31.0)	30.5 (27.2, 33.8)	0.85 (0.67, 1.08) p=0.18
	Secondary Analysis			
	Time to recovery *Median, days (95% CI)*	10.0 (9.0, 11.0)	11.0 (10.0,12.0)	1.11 (0.99, 1.24) p=0.15

	Odds of overall improvement on the NIAID OS <u>evaluated at Day 15</u> *Distribution across ordinal scale at Day 14*	-	-	1.28 (1.05, 1.56), p=0.02 (not multiplicity corrected)
	All-cause mortality by Day 29 *Number of deaths, n (%)*	62 (8.1)	100 (13.1)	0.57 (0.41, 0.78) p=0.002 (not multiplicity corrected)

*Table 35 Summary of efficacy for trial **RECOVERY***

<u>Title: Randomised Evaluation of COVID-19 Therapy (RECOVERY)</u>					
Study identifier	The RECOVERY trial is registered with ISRCTN (50189673) and clinicaltrials.gov (NCT04381936).				
Design	RECOVERY is a randomised, controlled, open-label platform trial, assessing multiple possible treatments in patients hospitalised for COVID-19.				
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		28 days not applicable 6 months		
Hypothesis	The null hypothesis is that there is no true difference in effect between any of the treatment arms				
Treatments groups	Baricitinib + SoC		SoC + baricitinib 4 mg once daily by mouth for 10 days or until discharge if sooner		
	SoC		SoC		
Endpoints	Primary endpoint	Mortality	All-cause mortality by day 28		
	Secondary endpoint	Discharge	Discharge from hospital within 28 days		
	Secondary endpoint	Invasive mechanical ventilation or death	Composite outcome of invasive mechanical ventilation (including extra-corporeal membrane oxygenation) or death, among patients not on invasive mechanical ventilation at randomisation		
Database lock	29 December 2021				
<u>Results and Analysis</u>					
Analysis description Primary Analysis					
Analysis population and time point description	Intention to Treat Population: all patients randomized, grouped according to the treatment assignment at randomization, irrespective of treatment received Time point: 28 days after randomization				
Descriptive statistics and estimate variability	Treatment group	Baricitinib + SoC	SoC alone		
	Number of subjects	4148	4008		
	28-day mortality (N (%))	513 (12.3%)	546 (13.6 %)		
Effect estimate per comparison	Primary endpoint – 28-day mortality	Comparison groups	Baricitinib + SoC vs. SoC alone		

Title: Randomised Evaluation of COVID-19 Therapy (RECOVERY)			
Study identifier	The RECOVERY trial is registered with ISRCTN (50189673) and clinicaltrials.gov (NCT04381936).		
		Time to event analysis using a log rank test; log-rank 'observed minus expected' statistic (and its variance) will be used to calculate the one-step estimate of the event rate ratio and confidence interval	0.9 (age-unadjusted RR)
		95% CI	0.80 - 1.02
		P-value	0.09
Analysis description Secondary Analysis			
	Discharge within 28 days	Comparison groups	Baricitinib + SoC vs. SoC alone
		Time to event analysis using log rank and calculation of event rate ratio as for the primary endpoint	1.1 (age-adjusted RR*)
		95% CI	1.04 - 1.15
		P-value	<0.001
	Invasive mechanical ventilation or death	Comparison groups	Baricitinib + SoC vs. SoC alone
		Risk ratio for pairwise comparison	0.9 (age-adjusted RR*)
		95% CI	0.81 – 0.99
		P-value	0.026
*Notes	Rate ratios for the secondary endpoints have been adjusted for age.		

2.5.4. Analysis performed across trials

Comparative analysis performed across ACTT-2 and KHAA

Both pivotal studies, ACTT-2 and KHAA were multicentre, double-blind, placebo-controlled, randomised studies. The study designs were generally consistent, with the following differences:

- Study ACTT-2 investigated baricitinib in combination with remdesivir, while Study KHAA investigated baricitinib + SOC per local guidelines, with approximately 20% of patients receiving remdesivir in Study KHAA.
- Use of corticosteroids was limited in Study ACTT-2 (only permitted for other standard indications including asthma exacerbation, ARDS, etc.), resulting in approximately 20% receiving corticosteroids at baseline or during the study. Study KHAA enrolled mainly after dexamethasone was widely adopted into clinical treatment guidelines for COVID-19 and 80% of patients were on corticosteroids for treatment of COVID-19 at baseline.
- The primary objective of each study is different; each study's primary objective is evaluated as a secondary objective of the other study:
    - time to recovery is the primary endpoint for Study ACTT-2 and is a multiplicity-controlled key secondary endpoint for Study KHAA;
    - the proportion of patients progressed to ventilation or death is the primary endpoint for Study KHAA and is a multiplicity-controlled key secondary endpoint for Study ACTT-2 per Study ACTT-2 Addendum SAP.

- Study ACTT-2 included patients with OS 4, 5, 6, and 7, while Study KHAA enrolled hospitalised patients with OS 4, 5, and 6. In Study KHAA, patients were required to have at least 1 instance of elevation in at least 1 inflammatory marker (CRP, D-dimer, LDH, or ferritin).
- Study ACTT-2 included mostly (approximately 90%) of patients from the US, while Study KHAA enrolled a diverse patient population including approximately 80% patients from outside the US (including 9% of patients from Europe), 20% of patients from the US, and. Aside from the US and the EU, Study KHAA also enrolled large numbers of patients from Brazil (22.1%), Mexico (18.4%), Argentina (13.6%), and Russia (7.3%).

Also, for both Studies ACTT-2 and KHAA:

  - The NIAID OS was used to classify baseline disease severity;

Patients were eligible for enrolment if they were in 1 of the following categories:

  - OS 4 hospitalised, not requiring supplemental oxygen (Study ACTT-2 and until amendment d for KHAA),
  - OS 5 hospitalised, requiring supplemental oxygen,
  - OS 6 hospitalised, on noninvasive ventilation/high-flow oxygen devices, or
  - OS 7 hospitalised, on invasive mechanical ventilation or ECMO (Study ACTT-2 only).

Table 36 Summary of Key Efficacy Results Study ACTT-2 (Combination with Remdesivir) and Study I4V-MC-KHAA (Baricitinib plus Standard of Care)

Endpoint Measure	**Study ACTT-2** **As-Treated Population** **Baseline OS 4,5,6,7**	**Study KHAA** **ITT Population** **Baseline OS 4,5,6**
Median time to recovery in days *(Study ACTT-2 Primary; Study KHAA Key Secondary)*	12.5% relative reduction (from 8 to 7 days) Rate ratio = 1.15 (1.00, 1.32) p=0.04	9.1% relative reduction (from 11 to 10 days) Rate ratio = 1.11 (0.99, 1.24) p=0.15[a] (not multiplicity-controlled)
Proportion of patients who died or progress to require noninvasive ventilation/high-flow oxygen or invasive mechanical ventilation (including ECMO) *(Study KHAA Primary; Study ACTT-2 Secondary)*	20.7% relative reduction (29% PBO + REM, 23% BARI + REM) OR = 0.73 (0.55, 0.97) p=0.03 (multiplicity-controlled)	8.9% relative reduction (30.5% PBO + SOC, 27.8% BARI + SOC) OR = 0.85 (0.67, 1.08) p=0.18
All-cause mortality *(Study ACTT-2 and Study KHAA Secondary)*	38.4% relative reduction[b] (7.3% PBO + REM, 4.5% BARI + REM) HR = 0.63 (0.37, 1.05) p=0.08 (multiplicity-controlled)	38.2% relative reduction (13.1% PBO + SOC, 8.1% BARI + SOC) HR = 0.57 (0.41, 0.78) Nominal p=0.002[a] (not multiplicity-controlled)
Likelihood of overall improvement on the NIAID OS *(Study ACTT-2 and Study KHAA Secondary)*	26% greater odds at Day 15 OR = 1.26 (1.01, 1.58) p=0.04 (multiplicity-controlled)	28% greater odds at Day 14: OR = 1.28 (1.05,1.56) p=0.02[a] (not multiplicity-controlled)

Abbreviations: BARI = baricitinib; ECMO = extracorporeal membrane oxygenation; HR = hazard ratio; ITT = intent-to-treat; NIAID OS = National Institute of Allergy and Infectious Diseases Ordinal Scale; OR = odds ratio; PBO = placebo; REM = remdesivir; SOC = standard of care.

a For Study KHAA, p-values are not adjusted for multiplicity.

b Study was not powered for assessment of mortality.

CHMP' assessment

Effect sizes were limited and statistical significance was not met for all endpoints, however consistency was observed in the favourable effects of baricitinib across both trials. Regarding the proportion of patients who died or progressed to ventilation, a larger effect size was observed in the ACTT-2 study. A possible explanation for this observation might be sought in the difference between the two trials in the concomitant use of corticosteroids, with baricitinib resulting in a smaller/add-on effect on top of corticosteroids in KHAA, where 80% of patients also used corticosteroids.

In the topline results of the RECOVERY trial, favourable effects can also be observed for the primary endpoint of D28 mortality and secondary endpoints of discharge alive within 28 days and the composite of reaching the event of mechanical ventilation or death. However, effect sizes are limited and statistical significance is not reached for the primary endpoint unadjusted for age. For an overview of outcomes of the three different studies, please refer to the table below.

	ACTT-2		KHAA		Recovery	
Endpoints	**Bari + REM (n=515)**	**PBO + REM (n=518)**	**Bari + SOC N=764**	**PBO + SOC N=761**	**Bari + SOC N=4148**	**SOC N=4008**
Median time to recovery (days)	7 (6, 8)	8 (7, 9)	10 (9, 11)	11 (10, 12)	*Discharge alive within 28Days* 8 [5 to 17]	8 [5 to 20]
Rate ratio (95% CI)	1.15 (1.00, 1.31) p=0.047		1.11 (0.99, 1.24) p=0.1453		*Age-adjusted RR* 1.1 (1.04-1.15) P<0.001	
Overall improvement in OS at day 15	1.26 (1.01, 1.57); p= 0.044		1.28 (1.05, 1.56) p= 0.0168			
Proportion of patients who died or progressed high flow oxygen or ventilation by Day 29; Odds Ratio (95% CI)	0.74 (0.56, 0.99) p= 0.039		0.85 (0.67, 1.08) p= 0.1800		*Composite of mechanical ventilation or death* *Age-adjusted RR* 0.9 (0.81- 0.99) P=0.026	
Mortality, Overall D28; KM Estimate (%)	5.1%	7.8%	8.1%	13.1%	12,4%	13.6%
HR (95% CI)	0.65 (0.39, 1.09) p=0.102		0.57 (0.41, 0.78) p=0.0018		*Un-adjusted RR* 0.9 (0.80, 1.02) P=0.09	

The RECOVERY trial report further refers to a meta-analysis of the treatment effect of JAK inhibitors suggesting an overall efficacy (RR) of 0.80, (95% CI 0.71−0.89). Restricting the meta-analysis to RECOVERY plus the 3 other baricitinib trials, the RR would be 0.81 (95% CI 0.73-0.91). Even though these results are appreciated, they are considered inadequate to support the assessment of B/R, given important deviations from the data and analysis standards required for regulatory assessment. Such deviations are related to (but not limited to) the lack of i) a protocol for the meta-analysis ii) a comprehensive and prospectively defined way of handling heterogeneity iii) detailed description of the PICOS criteria of the included studies. For further details with respect to the points to consider when submitting a meta-analysis as evidence please see CPMP/EWP/2330/99.

2.5.5. Clinical studies in special populations

No dedicated clinical studies have been performed in special populations.

In the ACTT-2 and the KHAA trial, the **elderly** population was included with people aged ≥ 65 years, comprising 30% and 32.7% of the respective study populations.

Baricitinib was initially proposed to be indicated for the treatment of coronavirus disease 2019 (COVID-19) in hospitalised adult and **paediatric** patients aged 10 years and older who require low-flow oxygen or noninvasive ventilation/high-flow oxygen.

A clinical trial is planned in paediatric patients hospitalised with COVID-19 who require supplemental oxygen to support registration in patients 1 to 10 years of age.

CHMP' assessment

The MAH has not conducted clinical trials in special populations, including the paediatric population. In response to the MO on inclusion of paediatric patients in the indication statement, the proposed indication has been limited to the adult population.

Elderly subjects aged 65 years and older were included in the pivotal trials, and primary efficacy results were comparable to results in the overall study population. The number of deaths across age groups, in both ACTT-2 and KHAA, was consistently lower for the baricitinib treated group compared to placebo, except for the group of patients over 85 years in Study KHAA. Data from both studies combined show no differences in the frequency of death reported for those >85 years of age for baricitinib treated patients (28.1%, n=9) and placebo (28%, n=7). In Study KHAA, 8 deaths were reported in the baricitinib treated group versus 3 in the placebo treated group, which is in contrast to what was reported by the ACTT-2 Study (1 death in the baricitinib treated group versus 4 in the placebo treated group). In the RECOVERY trial, no treatment effect was observed in patients aged older than 80 years (in both the baricitinib arm (130/341) and the SoC arm (102/267) 38% of patients died. (RR 1.01; 95%CI 0.78 – 1.31). Taking into account the divergent results on efficacy in the population aged above 80 years as observed in the three trials, the MAH is requested to discuss efficacy in this population and to present a proposal on how this could be reflected in SPC section 5.1.

2.5.6. Supportive studies

ACTT-4

This is a randomised phase 3 study NIAID-sponsored study, of which the MAH received the top-line, preliminary results through Day 29 on 30 June 2021. The Clinical Study Report for Study ACTT-4 is expected to become available in Quarter 4, 2021. NIAID has confirmed permission to share this top-line data with regulatory authorities.

Design of Study ACTT-4

Study ACTT-4 randomised 1010 adult patients hospitalised with COVID-19 and requiring supplemental oxygen (oxygen administered by low-flow [OS 5], high-flow, or noninvasive mechanical ventilation modalities [OS 6]) to either the combination of baricitinib + remdesivir (n = 516) or dexamethasone + remdesivir (n = 494). Patients were excluded if they required invasive mechanical ventilation at the time of randomisation. The study was conducted in Japan, Mexico, Singapore, South Korea, and the US, with the US enrolling approximately 90% of the patients.

The primary objective was to evaluate the clinical efficacy between baricitinib + remdesivir and dexamethasone + remdesivir, as assessed by mechanical ventilation-free survival by Day 29 (defined as the proportion of subjects not meeting criteria for 1 of the following 2 ordinal scale categories at any time by Day 29 [NIAID OS 8: Death; NIAID OS 7: Hospitalised, on invasive mechanical ventilation or ECMO]). The primary efficacy analysis was a test of superiority between the 2 treatment groups.

Secondary endpoints included mortality, time to recovery (NIAID OS 3 or lower), and overall improvement on the NIAID OS.

The primary efficacy analysis was performed on the modified intent-to-treat (mITT) Population. The mITT Population included all randomised patients. These patients were classified by their randomised treatment assignment and *actual baseline clinical status* (as opposed to the Intent-to-Treat [ITT] Population, in which patients were classified by their *randomised disease severity stratum*).

The study closed enrolment on 13 April 2021, as the study met predefined futility criteria indicating that neither treatment regimen studied was likely significantly better than the other.

Efficacy in Study ACTT-4

The primary endpoint of the study (superiority of 1 group versus another) was not met since a similar proportion of patients either died or required mechanical ventilation by Day 29 in the baricitinib + remdesivir group compared with the dexamethasone + remdesivir group (HR 0.94 [95% CI: 0.66, 1.34]; p=0.909).

Although there was a smaller proportion of patients who died by Day 29 in the baricitinib + remdesivir group compared with the dexamethasone + remdesivir group (5.2% versus 6.1%, respectively), this was not statistically significant.

Time to recovery and the odds of clinical improvement on the NIAID OS by Day 15 were both similar between the treatment groups.

Table 37 Efficacy outcomes in study ACTT-4: modified intent-to-treat population – patients with baseline NIAID OS 5 or 6

	Dexamethasone + Remdesivir (N = 494)	Baricitinib + Remdesivir (N = 515)
Mechanical ventilation-free survival by Day 29		
Progression to death or mechanical ventilation, n (%)	58 (11.7)	65 (12.6)
KM estimate of non-progression (95% CI)	0.88 (0.84, 0.90)	0.87 (0.84, 0.90)
HR (95% CI)[a]		0.94 (0.66, 1.34)
p-Value[b]		0.909
All-cause mortality by Day 29		
Deaths, n (%)	30 (6.1)	27 (5.2)
KM estimate (95% CI)	0.06 (0.05, 0.09)	0.05 (0.04, 0.08)
HR (95% CI)		1.21 (0.72, 2.04)
p-Value[c]		0.465
Time to recovery by Day 29		
Recoveries, n (%)	428 (86.6)	442 (85.8)
Median time to recovery, days (95% CI)	5.0 (5.0, 6.0)	6.0 (5.0, 6.0)
HR (95% CI)[a]		1.04 (0.91, 1.19)
Clinical improvement on the NIAID OS by Day 15		
Odds ratio (95% CI)		1.01 (0.80, 1.27)

Conclusion

In Study ACTT-4, baricitinib in combination with remdesivir provided similar efficacy to dexamethasone in combination with remdesivir in OS 5 and OS 6 hospitalised patients.

CHMP' assessment

While the topline results of the ACTT-4 trial (comparing baricitinib with corticosteroids on a background regimen of remdesivir) may be acknowledged, this trial was designed to demonstrate superiority and prematurely halted for futility when no significant benefit for one of both therapies could be observed. Based upon the current description on the ACTT-4 trial and the accompanying SAP and futility analysis plan, no formal test for non-inferiority of baricitinib as compared to corticosteroids has been performed (or was planned) and therefore no definite conclusions can be drawn.

2.5.7. Discussion on clinical efficacy

Baricitinib is a Janus kinase (JAK) inhibitor and blocks extracellular signals from multiple cytokines that are thought to contribute to inflammation and worsening of COVID-19. It is currently registered for the treatment of rheumatoid arthritis, atopic dermatitis and alopecia areata in adults. The MAH initially claimed the following therapeutic indication:

"Olumiant is indicated for the treatment of coronavirus disease 2019 (COVID 19) in hospitalised adult and paediatric patients aged 10 years and older who require low-flow oxygen or non-invasive ventilation/high flow oxygen (see section 5.1)."

Two pivotal studies have been performed with baricitinib to support the extension of the indication (EoI), the ACTT-2 study and the KHAA/COV-BARRIER study. No formal scientific advice has been sought with the CHMP on the proposed EoI.

Upon CHMP request and in response to the first request for supplementary information, the indication was limited to the adult population as no clinical and pharmacokinetic data were provided for the paediatric population. in addition, topline results in patients with baseline OS 7 included in the KHAA trial per addendum 5 and topline results of the ACTT-4 trial were provided with this response.

In response to the CHMP MO on clinical efficacy that has been raised in the second request for supplementary information, topline results of the baricitinib arm of the RECOVERY trial have been provided.

Design and conduct of clinical studies

Design

Both the ACTT-2 and KHAA were multicentre, randomized, blinded, placebo-controlled Phase 3 trials. ACTT-2 (Date of the first enrolment: 08 May 2020. Date of the last visit: 31 July 2020) evaluated efficacy and safety of baricitinib and placebo on a background regimen of remdesivir. Around 20% of patients received concomitant corticosteroids. KHAA evaluated the efficacy and safety of baricitinib and placebo on a background regimen of local SOC. During enrolment for KHAA (Date of first enrolment 11 Jun 2020; Date of last visit (Day 28): 12 Feb 2021), corticosteroid treatment was adopted as the standard of care (SOC), and around 80% of patients were on corticosteroids for the treatment of COVID-19 at baseline. In both studies, baricitinib was given as an oral dose of 4 mg daily (currently registered dose) for the duration of hospitalisation up to Day 14. In the ACTT-2 study, remdesivir was given as a loading dose of remdesivir 200 mg IV, followed by 100 mg IV for the duration of hospitalisation up to Day 10. The NIAID ordinal scale (OS) was used for the assessment of clinical status in both studies.

Endpoints

Where time to recovery is the primary endpoint for Study ACTT-2, it is a secondary endpoint for Study KHAA. Conversely, the proportion of patients who progressed to ventilation or death is the primary

endpoint for Study KHAA and is a secondary endpoint for Study ACTT-2. Although the time to recovery is an accepted endpoint for COVID-19 treatment studies, the clinical relevance of this endpoint could be debated since initial recovery may be followed by clinical relapse and time to sustained recovery would have been preferred. These data were provided upon request (see also below).

Whilst disease progression is considered to be clinically relevant, this primary endpoint by definition only takes into account the first event of disease progression and does not provide any information on what happened to patients after this first event. A further breakdown of the data illustrating what happened to patients after their first event of progression has been requested (see also below). Apart from time to recovery and disease progression, the MAH added multiple secondary endpoints, of which all-cause mortality by Day 29 and odds for clinical improvement by Day 15 were complementary endpoints for both studies. Overall, all-cause mortality is considered the most robust and clinically relevant endpoint for the assessment of this procedure.

Study participants

Both studies included adult hospitalised patients with laboratory-confirmed SARS-CoV-2 infection. Study ACTT-2 included patients with OS 4, 5, 6, and 7, while Study KHAA initially enrolled hospitalised patients with OS 4, 5, and 6. With an amendment of the KHAA protocol during enrolment, patients with OS 4 were no longer included as these patients were less likely to contribute to the primary outcome measure of disease progression, which is considered acceptable given that the sought indication is patients who require low-flow oxygen or non-invasive ventilation/high flow oxygen. Further, an addendum to the protocol of the KHAA trial includes patients with baseline OS 7. A summary of efficacy results has been provided with the responses to the first RSI, while a CSR Addendum summarising data from Study KHAA Addendum 5 is expected to be available in late Quarter 3 or Quarter 4, 2021. The MAH is requested to provide the D60 results of the KHAA trial (final CSR, including baseline OS 7 results). Overall, the in- and exclusion criteria of both studies are considered to be appropriate and to result in a population-representative for the adult population envisioned.

Conduct of the studies

Overall, the conduct of the studies is considered acceptable. However, in ACTT-2 forty-four stratification errors for disease severity (assignment to baseline scale 5 instead of 6 and vice versa) occurred at the time of randomization. As a single site was responsible for 32 errors, analyses of the primary and secondary endpoints by ordinal scale excluding this site have been requested.

Efficacy data and additional analyses

Main results

ACTT-2 included a total of 1033 subjects, 515 subjects randomised to baricitinib + remdesivir and 518 subjects randomised to placebo + remdesivir. KHAA included 1525 patients, 764 randomised to baricitinib and 761 randomised to placebo. Most subjects included in the ITT population of both studies were white males aged between 40 and 64 years. Most subjects had one or more comorbidities at enrolment, with obesity, hypertension and diabetes mellitus most commonly reported. In ACTT-2, 11% of patients had a baseline clinical status of 7, 21% had a clinical status of 6, 55% had a clinical status of 5 and 14% had a clinical status of 4. In KHAA, 24.4% of patients had a clinical status of 6, 63.4% of patients had a clinical status of 5 and 12.3% of patients had a clinical status of 4. Overall, baseline characteristics were well balanced across the two arms of both studies.

In the ACTT-2 trial, statistical significance was met for time to recovery (primary endpoint), which was shortened by one day in patients treated with baricitinib. The median time to recovery was 7 days (95% CI: 6.0, 8.0) compared to 8 days (95% CI: 7.0, 9.0) in the baricitinib + remdesivir and placebo +

remdesivir groups respectively (rate ratio (RR) for recovery 1.16; 95% CI 1.01- 1.33; p=0.03). The one day improvement of time to recovery, that was only marginally statistically significant, is of unknown clinical relevance. An analysis of time to sustained recovery has been requested. In their response, the MAH provided a sensitivity analysis censoring patients who were readmitted after initial recovery. Time to recovery after censoring readmittance still showed a numerical benefit for the baricitinib + remdesivir group over the placebo + remdesivir group that was consistent with the analysis of the primary endpoint as depicted in the ACTT-2 CSR; median time to recovery in this sensitivity analysis: baricitinib + remdesivir = 7.0 days, placebo + remdesivir = 8.0 days, hazard ratio (HR) 1.13, 95% CI 0.98 to 1.29), but significance was not reached. The proportion of recovered patients that reached a sustained recovery status was marginally larger in the placebo group. These observations further illustrate that the observed effect in the primary outcome was already limited as the small number of patients censored for the sensitivity analysis, results in the difference between the groups being no longer statistically significant. Moreover, a substantial part of the study population did not recover and did not die by Day 29 (16% in the baricitinib vs 22% in the placebo group). Upon request, the MAH has explained that for ACTT-2, no data are available after Day 29 and thus uncertainty remains regarding the large proportion of patients for whom clinical status is not known (n=x% in both groups)In ACTT-2, a significantly smaller proportion of patients treated with baricitinib + remdesivir compared to patients treated with placebo + remdesivir died or progressed to ventilation (23% vs 29%; OR 0.73; p = 0.03). For all-cause mortality by Day 29: a numerical reduction in mortality was observed in the baricitinib group, with mortality rates of 4.5% for baricitinib + remdesivir versus 7.3% for placebo + remdesivir (HR = 0.63 [95% CI: 0.37, 1.05]; p=0.075). However, this difference was not statistically significant. Of note, the results of the analyses leaving out the site with 32 stratification errors, are consistent with the results for the full As-Treated population.

The KHAA trial failed to meet its primary endpoint, although a numerical trend towards less disease progression in the baricitinib group was observed. The proportion of patients who progressed to ventilation or death was 30.5% (27.2, 33.8) for placebo-treated patients and 27.8% (24.6, 31.0) for baricitinib treated patients (OR for disease progression 0.85; 95%CI 0.67- 1.08; p=0.18). The MHA has provided a further breakdown of the data after the initial event of progression; no new concerns arise with respect to consistency of the observed results. In KHAA, time to recovery was again shortened by one day in patients treated with baricitinib, in line with the observation in ACTT-2. The median time to recovery was 10 days in the baricitinib + SOC group and 11 days in the placebo + SOC group (RR 1.11; 95% CI 0.99 - 1.24]). Also in KHAA, a reduction in Day 28 all-cause mortality was observed with mortality rates of 8.1% for baricitinib versus 13.1% for placebo-treated patients (38.2% relative reduction; HR = 0.57 [95% CI 0.41 - 0.78], p=0.002 (not multiplicity-controlled)). As Study KHAA did not meet its primary objective, none of the secondary endpoints met multiplicity-controlled statistical significance.

Although effect sizes were limited and statistical significance was not met for all endpoints, consistency was observed in the favourable effects of baricitinib across both pivotal trials. All-cause mortality results are considered to be of most clinical relevance. A 38% relative reduction in all-cause mortality was observed in both studies, illustrating a probable beneficial effect of baricitinib in patents hospitalized with COVID-19 in need of supplemental oxygen. The clinical relevance of mortality as outcome is thus not debated. However, the statistical robustness of the results remains questionable.

Subgroup analysis

For both studies the results for the primary efficacy endpoints were generally consistent across subgroups of age, sex, weight, duration of symptoms and comorbidities.

Baseline disease severity

In ACTT-2 the reduction in time to recovery observed for the overall population is mainly driven by the beneficial effect observed in baseline ordinal scale 6 (HR 1.52; 95%CI 1.11-2.06) and to a lesser extent, baseline ordinal scale 5 (HR 1.17; 95%CI 1.00-1.37). Also for the secondary outcome measures of progression to ventilation or death and all-cause mortality, a beneficial effect is mainly observed for baseline ordinal scale categories 6 and 5.

In KHAA the numerical reduction in the proportion of patients progressing to ventilation or death is observed for all baseline ordinal scale categories: 6 (OR 0.85; 95%CI 0.56-1.30), 5 (OR 0.87; 95%CI 0.65-1.17) and 4 (OR 0.78; 95%CI 0.27, 2.22). For the secondary outcome measure of time to recovery, benefit is only observed in baseline ordinal scale 6, and for all-cause mortality, the main benefit is observed in baseline ordinal scale 6 and baseline ordinal scale 5 to a lesser extent.

Results in baseline OS categories 4 and 7 were less consistent. As the proposed indication for treatment of COVID-19 is limited to patients in baseline ordinal scales 5 and 6, this has been adequately reflected in the indication statement.

Concomitant corticosteroid treatment

When ACTT-2 was performed, corticosteroids were not used as SOC for the treatment of COVID-19, reflected by the small number of patients who received corticosteroids in this study (around 22%).

In KHAA, 79.3% of the patients received systemic corticosteroids at baseline. The numerical improvement with fewer patients progressing to ventilation or death in the baricitinib group was observed (in the logistic regression analysis) whether baricitinib was taken with or without corticosteroids, indicating that baricitinib has a beneficial effect also on top of corticosteroid treatment in the overall population. The OR (95%CI) for disease progression was 0.92 (0.51-1.67) for the corticosteroid use "no" group and 0.83 (0.65-1.07) for the corticosteroid use "yes" group. However, in Population 2 (patients requiring supp oxygen who did not receive baseline corticosteroids, N = 205) an adverse effect was observed with 1.7% more patients progressing in the baricitinib + SOC group as compared to the placebo + SOC group (28.9% vs 27.1%). Further analyses have been performed to exclude that this difference was introduced by a difference in baseline disease severity (no patients with baseline OS 4 were included in Population 2).No difference was observed in the treatment effect for patients without corticosteroids at baseline between patients in baseline scales 4 (no oxygen) vs baseline scales 5 and 6 (suppl oxygen). Thus at this stage, there is no reasonable explanation for the adverse results on the primary outcome measure in Population 2, with more patients progressing in the baricitinib group.

Special populations

No dedicated studies were performed in special populations. Elderly subjects aged 65 years and older, were included in the pivotal trials and primary efficacy results for patients aged older than 65 were comparable to results in the overall study population. In patients aged above 80 to 85 years, the observed treatment effect is not unequivocal which should to be addressed in SmPC section 5.1.

Initially, the proposed indication statement, included treatment of paediatric patients aged 10 years and older. As no clinical and pharmacokinetic data were provided for the paediatric population, inclusion of the paediatric population in the indication statement was considered not acceptable by the CHMP and a major objection (MO) was raised. In their response, the MAH submitted a revised product information with an indication limited to the adult population.

Supportive data

In response to the CHMP MO on clinical efficacy that has been raised in the first round of assessment, the MAH refers to supportive evidence coming from patients with baseline OS 7 that were included in

the KHAA trial per addendum 5 (topline efficacy data for this subgroup became available recently and indicate that Day 28 mortality was significantly reduced in the baricitinib group as compared to placebo) and to the topline results of the ACTT-4. The ACTT-4 is a randomized phase 3 superiority trial, comparing baricitinib + remdesivir with dexamethasone + remdesivir in the treatment of patients hospitalized with COVID-19. Enrolment was closed prematurely, as the study met predefined futility criteria indicating that neither treatment regimen studied was likely significantly better than the other. The primary endpoint of the study (superiority of 1 group versus another) was not met since a similar proportion of patients either died or required mechanical ventilation by Day 29 in the baricitinib + remdesivir group compared with the dexamethasone + remdesivir group (by Day 29 5.2% of patients in the baricitinib + remdesivir group had died as compared to 6.1% in the dexamethasone + remdesivir group). Time to recovery and the odds of clinical improvement on the NIAID OS by Day 15 were both similar between the treatment groups. Based upon these findings, the MAH states that in ACTT-4 baricitinib in combination with remdesivir provided similar efficacy to dexamethasone in combination with remdesivir in OS 5 and OS 6 hospitalised patients.

Although it is agreed with the MAH that the observed reduction in mortality in patients with baseline OS 7 (included per addendum 5 of the KHAA study) further supports the potential benefit in mortality that may be observed in other baseline OS subgroups in this study, these data do not alleviate CHMP's concern regarding the overall strength of evidence obtained from KHAA. Moreover, mortality in baseline OS 7 in study ACTT-2 was not significantly different between treatment arms and results for this subgroup thus remain inconclusive.

Similarly, the topline results of the ACTT-4 trial (comparing baricitinib with corticosteroids on a background regimen of remdesivir) may be acknowledged, but this trial was designed to demonstrate superiority and was prematurely halted for futility when no significant benefit for one of both therapies could be observed. Neither the possibility for testing for equivalence (or non-inferiority) nor an equivalence (or non-inferiority) margin has been pre-defined. Therefore inference with respect to such goals is not appropriate. One of the requirements for switching of such kind of a trial objective is that the non-inferiority margin with respect to the control treatment was pre-defined or can be justified. (The latter is likely to prove difficult and to be limited to rare cases where there is a widely accepted value for Δ.) – (CPMP/EWP/482/99, POINTS TO CONSIDER ON SWITCHING BETWEEN SUPERIORITY AND NON-INFERIORITY). Thus, this trial does not provide the confirmatory evidence that is considered needed to ensure baricitinib really has a beneficial effect for patients with COVID-19 in need of oxygen.

RECOVERY TRIAL

In response to the CHMP MO on clinical efficacy that has been raised in the second request for supplementary information, topline results of the baricitinib arm of the RECOVERY trial have been provided. The RECOVERY trial is a randomised, controlled, open-label platform trial, assessing multiple possible treatments in patients hospitalised for COVID-19. The adaptive design of the RECOVERY trial allows for new trial arms to be added as evidence emerges that other candidate therapeutics should be evaluated. To facilitate collaboration during the COVID-19 pandemic, trial procedures were greatly streamlined. Although it is acknowledged that the trial was designed during the COVID-19 pandemic to allow for a fast evaluation of different drugs, its design limits the interpretability of the study results.

All RECOVERY trial participants received usual standard of care. Upon study entry, a single participant could be randomised to receive different treatments on top of usual standard of care. Consenting patients eligible for baricitinib treatment, were assigned in a 1:1 ratio to either usual SoC plus baricitinib 4 mg once daily, or usual SoC alone. Randomization was not stratified which may have impacted the study results.

The primary endpoint of the RECOVERY trial was D28 all-cause mortality, which is considered a robust and clinically relevant outcome measure. The secondary endpoints -discharge alive within 28 days and the composite outcome of invasive mechanical ventilation or death- provide further insight into the efficacy of baricitinib in the treatment of COVID-19.

The sample size was not predefined and was adaptively evaluated in a blinded fashion. Recruitment was closed when over 8150 patients had been randomised and the blinded 28-day mortality rate was 12.9% (suggesting there would be at least 1050 deaths), giving at least 90% power to detect a proportional risk reduction in the primary outcome of one-fifth at 2P=0.01. The Trial Steering Committee and all other individuals involved in the trial were masked to outcome data until after the close of recruitment. Given the pandemic setting this approach can be accepted. However, it should be noted that the intended level of significance at which the primary analysis is to be performed is not entirely clear. In the SAP, it is mentioned that *"Evaluation of the primary trial (main randomisation) and secondary randomisation will be conducted independently, and no adjustment be made for these. Formal adjustment will not be made for multiple treatment comparisons, the testing of secondary and subsidiary outcomes, or subgroup analyses (with one exception; see Appendix A). However, due allowance for multiple testing will be made in the interpretation of the results: the larger the number of events on which a comparison is based and the more extreme the P-value after any allowance has been made for the nature of the particular comparison (i.e. primary or secondary; pre-specified or exploratory), the more reliable the comparison and, hence, the more definite any finding will be considered. 95% confidence intervals will be presented for the main comparisons."* Even though the 95% CI could be read as implying a prospectively defined 5% two-sided significance level, it refers to *all* ("main") comparisons, which makes interpretation less straightforward. It is furthermore implied that the level of evidence will depend on the amount of information in which a comparison will be based. Furthermore, at the timing of recruitment closing, and in a blinded fashion, a two-sided significance level of 0.01 is introduced, at which a 90% power was calculated. Given the relatively large sample size, this level of significance would be considered appropriate.

During enrolment for baricitinib, 4148 patients were randomly allocated to baricitinib and 4008 were randomly allocated to usual care. Strikingly, only 3734 of 4148 patients (90%) allocated to receive baricitinib, were actually treated with baricitinib, while 11 of 4008 patients (0.02%) randomized to SoC received baricitinib. Baseline disease characteristics of the evaluated ITT population were very well balanced across treatment arms. Per study protocol, the primary analysis was performed in the ITT population and thus included 4148 patients in the baricitinib arm and 4008 patients in the SoC arm, of whom 513 (12.4%) and 546 (13.6%) of patients had died by Day 28. Although with a limited effect size, a reduction in 28-day mortality of 1.2% was observed in patients treated with baricitinib. The proportional effect of baricitinib on mortality was consistent across pre-specified subgroups, except for patients aged older than 80 years in whom no benefit in D28 mortality was observed and for the very small group of patients who did not receive corticosteroids at baseline in whom there seems to be a small opposite effect, though with large uncertainty. The effect of baricitinib was also comparable across posthoc defined subgroups categorized by CRP, tocilizumab use and remdesivir use.

Notably, the difference between the groups only became statistically significant after adjustment for age or after adjustment for all prespecified co-variates (age, sex, race, respiratory support, days since symptom onset) (please refer to section on Outcomes/Endpoints above). The MAH presents the age-adjusted RR as the primary analysis supporting efficacy. However, the prospective nature of this analysis is not justified. In the statistical analysis plan for the RECOVERY trial, it is mentioned that *"The main analyses described above will be unadjusted for baseline characteristics. However, if there are any important imbalances between the randomised groups in key baseline prespecified subgroups or*

allocation in the orthogonal components of the main randomisation, where applicable, emphasis will be placed on analyses that are adjusted for the relevant baseline characteristic(s). This will be done using Cox regression for the estimation of adjusted hazard ratios and a log-binomial regression model for the estimation of adjusted risk ratios." Neither "any important imbalances" nor "emphasis will be placed" have been further specified. While from a clinical point of view age as a prognostic factor for COVID-19 is acknowledged, there was only a marginal difference in mean age of 0.8 years with standard deviations largely overlapping (mean age baricitinib group 58.5 years (SD 15.4) and mean age SoC group 57.7 years (SD 15.5)). Thus, the choice of age as the controlling variable on which the primary analysis is based is not justified. Furthermore, the "imbalance" of 0.8 years difference in mean age between groups is not reflected in the categorical variable describing different age categories, in which the imbalance is of no larger magnitude than any other prognostic variables for which corrected analyses were thought to be of relevance. However, the categorical age variable is chosen as the one used for correction in the main analysis. Given the lack of clearly pre-specified conditions for an adjusted analysis and the discrepancy between the variable on which "imbalance" is observed (continuous age) and the variable on which the corrected estimate is based (age categories), the age-adjusted RR is not acceptable as a primary efficacy measure. Thus the unadjusted analysis is considered the main analysis and its outcome does not reach statistical significance. The uncertainty surrounding the conclusion of efficacy of baricitinib is further perplexed by the significance level to be employed in the main analysis (see above). In addition to the concerns raised with respect to the adjusted analysis, it should be noted that the significance level of 0.01, implied by the decision to stop recruitment, is not reached, even with the age-adjusted analysis.

Strikingly, 10% of patients allocated to baricitinib did not receive baricitinib (414 out of 4148). Upon request, the MAH indicated that the reason for these patients not receiving their allocated treatment is not known. It turned out that mortality in this subgroup was above 20% (data not shown here). The MAH is requested to present the baseline characteristics for patients not receiving their assigned treatment with baricitinib as compared to baseline characteristics of patients wo did receive their treatment with baricitinib and to discuss the reasons for the apparently high mortality rate in the group of patients that did not receive baricitinib treatment while assigned. (OC) Furthermore, it turned out that the data presented by the MAH are not the final RECOVERY data. Given the uncertainties surrounding the primary outcome measure, the final decision on this procedure should be based on all available data and hence the MAH should provide all analyses based on the updated datacut.

For the secondary endpoints, only age adjusted rate ratios have been provided, thus the results should be interpreted with caution. Patients treated with baricitinib had a significantly higher chance to be discharged alive within 28 days compared with usual care (80% vs. 78%; age-adjusted rate ratio 1·10, 95% CI 1·04 to 1·15; median 8 days [IQR 5 to 17] vs. 8 days [IQR 5 to 20]) and a lower risk of progressing to the composite secondary outcome of invasive mechanical ventilation or death (16% vs. 17%, age-adjusted risk ratio 0·90, 95% CI 0·81 to 0·99).

Overall, and in line with the ACTT-2 and COV-BARRIER results, the baricitinib RECOVERY data illustrate a small but consistent effect in favour of baricitinib across different clinically relevant outcome measures, including all-cause mortality at Day 28. However, focusing on the unadjusted analysis of Day 28 all-cause mortality as the primary analysis for this trial, the primary outcome of the study was not met. Moreover, the MAH indicated that an updated data cut is now available which implies that the data currently provided to EMA are not the final baricitinib data. Given the uncertainties surrounding the primary outcome measure, the final decision on this procedure should be based on all available data; hence the MAH should provide all analyses based on the updated data cut from RECOVERY which are now available. (OC)

Meta-analysis

The RECOVERY trial report further refers to a meta-analysis of the treatment effect of JAK inhibitors suggesting an overall efficacy (RR) of 0.80, (95% CI 0.71−0.89). Restricting the meta-analysis to RECOVERY plus the 3 other baricitinib trials, the RR would be 0.81 (95% CI 0.73-0.91). Even though these results are appreciated, they are considered inadequate to support the assessment of B/R, given important deviations from the data and analysis standards required for regulatory assessment. Such deviations are related to (but not limited to) the lack of i) a protocol for the meta-analysis ii) a comprehensive and prospectively defined way of handling heterogeneity iii) detailed description of the PICOS criteria of the included studies. For further details with respect to the points to consider when submitting a meta-analysis as evidence please see CPMP/EWP/2330/99.

WHO living guidelines
Further the MAH refers to the WHO recommendations on the use of baricitinib. Although WHO recommendations are acknowledged, these cannot be used as a basis for regulatory decision making.

2.5.8. Conclusions on clinical efficacy

In conclusion, the present application for a new indication in adult COVID-19 patients in need of supplemental oxygen has been based on one trial that met its primary endpoint (ACTT-2) and two trials that -according to regulatory standards- failed to meet their primary endpoints (KHAA and RECOVERY). Although the relevance of mortality as an outcome is not debated, the limited clinical relevance of the primary endpoint in ACTT-2 and the lack of statistical significance of the primary endpoints for KHAA and RECOVERY cannot be disregarded. These findings cannot be overcome by the results of the meta-analysis that has been performed for different JAK-inhibitors or by the WHO living guidelines for the treatment of COVID-19. In conclusion, the MO is considered unresolved at this stage and the MAH should provide all analyses based on the updated data cut from RECOVERY.

2.6. Clinical safety

Introduction

Olumiant is available as 2mg and 4mg tablets. It is currently indicated to treat adult Rheumatoid arthritis and adult Atopic dermatitis (it is referred to the SmPC for more details). The currently known safety profile, contra-indications and warnings, are coming from those two indications. Studies in the paediatric population (Atopic dermatitis, Juvenile idiopathic arthritis, but not Covid-19) are ongoing.

Contra-indications

Baricitinib is contra-indicated in **pregnancy** and in known cases of hypersensitivity to the active substance or any of the excipients.

Warnings

The SmPC includes warnings regarding the occurrence of infections, viral reactivation, haematological abnormalities, venous thromboembolism, lipids, hepatic transaminase elevations, malignancy, hypersensitivity, diverticulitis. The SmPC also includes warnings regarding vaccination, guidance for laboratory monitoring (lipids, absolute neutrophil count, absolute lymphocyte count, haemoglobin, hepatic transaminases), concomitant treatment with other immunosuppressive drugs.

Baricitinib is associated with an increased rate of **infections** such as upper respiratory tract infections compared to placebo. In patients with active, chronic or recurrent infections, the risks and benefits of treatment with Olumiant should be carefully considered. If an infection develops and the patient is not responding to standard therapy, treatment with baricitinib should be temporarily interrupted.

In relation to **haematological abnormalities**, treatment should not be initiated, or should be temporarily interrupted, in patients with an ANC < 1 x 10^9 cells/L, ALC < 0.5 x 10^9 cells/L or haemoglobin < 8 g/dL.

Cases of **viral reactivation**, including herpes virus reactivation, were reported in clinical studies.

Dose-dependent **increases in hepatic transaminase** (ALT and AST) were reported in patients treated with baricitinib compared to placebo. If drug-induced liver injury is suspected, treatment with baricitinib should be temporarily interrupted.

Events of **venous thromboembolism** (deep venous thrombosis and pulmonary embolism) have been reported in patients receiving baricitinib. Olumiant should be used with caution in patients with risk factors for DVT/PE, such as older age, obesity, a medical history of DVT/PE, or patients undergoing surgery and immobilisation. If clinical features of DVT/PE occur, Olumiant should be discontinued.

Unfavourable effects

In patients with Rheumatoid arthritis and with Atopic dermatitis, the most commonly reported Adverse drug reactions were increased LDL cholesterol, upper respiratory tract infections, and headache. Among the 'common' Adverse drug reactions are viral reactivation (herpes) and pneumonia, while deep venous thrombosis and pulmonary embolism were 'uncommon'.

Clinical studies

The safety experience of baricitinib for the treatment of hospitalised adult patients with Covid-19 is based on two randomised controlled trials: study ACTT-2 conducted by the NIH and study KHAA conducted by

Lilly. Study ACTT-2 has been completed, the safety follow-up of study KHAA up to Day 60 was completed in May 202. From a third clinical trial, ACTT-4, only top-line data became available around July 2021.

Study **ACTT-2** is a 'phase 3' randomised, double-blind, placebo-controlled trial to evaluate the efficacy and safety of 4-mg baricitinib + remdesivir versus placebo + remdesivir in hospitalised adult patients with COVID-19. The study was conducted in the US, EU, Singapore, South Korea, Mexico, and Japan. There were 1033 hospitalised adult patients enrolled; last-patient-last-visit occurred on 31 July 2020.

Study **KHAA** is a 'phase 3' randomised, double-blind, placebo-controlled trial to evaluate the efficacy and safety of baricitinib 4 mg in addition to standard-of-care (SOC) versus placebo and SOC in hospitalised adults with COVID-19 and at least one raised inflammation marker. The study was conducted in the US, EU, Asia, India, and Latin America. Standard-of-care therapies could include antimalarials, antivirals, and/or azithromycin, as well as corticosteroids. There were 1525 hospitalised adult patients enrolled.

Study **ACTT-4** is a 'phase 3' randomised, double-blind, placebo-controlled adaptive study to evaluate the efficacy and safety of baricitinib + remdesivir versus dexamethasone + remdesivir in hospitalised adults with COVID-19. Based on pre-planned futility analysis and review, NIAID closed enrolment with just more than 1000 participants. The DSMB determined there are no safety issues with either treatment regimen.

The **RECOVERY** study is a 'phase 3' randomised open-label study to evaluate the efficacy and safety of up to 10 days of oral baricitinib 4 mg in addition to usual care, versus usual care alone, in patients aged >2 years, who were hospitalised due to Covid-19. There were over 8150 patients enrolled.

Assessment of Adverse Events

Safety endpoints in studies ACTT-2 and KHAA included deaths due to AE up to and including Day 29 (Study ACTT-2) or Day 28 (Study KHAA), SAEs, AEs, and permanent discontinuations or temporary interruptions from study drug. Deaths due to any cause were analysed as an efficacy endpoint. Study ACTT-2 only collected severe or life-threatening AEs (grade 3 and 4), while Study KHAA collected mild, moderate, severe, or life-threatening AEs.

Populations analysed

In study ACTT-2, the Safety population included all patients who were randomised and received at least one dose of any investigational product.

In study KHAA, the Safety population included all participants randomly assigned to study intervention and who receive at least 1 dose of study intervention and who did not discontinue from the study for the reason 'Lost to Follow-up' at the first postbaseline visit. Participants were analysed according to the intervention they received.

CHMP's assessment

In study ACTT-2, only severe and life-threatening AEs (grade 3 and 4) were collected, while in study KHAA the AEs that were mild (grade 1), moderate (grade 2), severe, or life-threatening AEs were collected. In the context of short-term treatment of hospitalised patients with Covid-19, it is in principle acceptable that in ACTT-2 only grade 3 and 4 AEs were collected. This, however, means that the occurrence and potential as ADRs for grade 1 and 2 AEs must be estimated from trial KHAA only.

It is agreed that for the analysis of safety, the data of trials ACTT-2 and KHAA are pooled, as well as being presented separately. The primary analysis of safety commonly is on pooled data, which increases precision and reduces the number of comparisons. However, a major difference between the two trials is that in study ACTT-2, baricitinib is compared to placebo on a background of remdesivir,

while in study KHAA this comparison is performed against a background of 'standard-of-care', which usually (~80%) was corticosteroids. The design of the studies was similar. Also, based on their mechanism of action, drug-drug interactions of baricitinib with corticosteroids and with remdesivir are not expected. The pooled safety results should be checked against the individual trial results, especially if AEs are also ADRs of remdesivir (e.g. transaminases increased) or corticosteroids (e.g. transaminases increased, pneumonia, neutropenia, VTE).

The period of exposure to the study drug (up to 14 days) is about half of the observation time of safety events (28 to 29 days). The half-life of baricitinib on average is 12 hours, and after 3-4 days (7 times the half-life) it can be safely assumed that baricitinib is not present anymore in most individuals. PD effects for safety events may have different time windows after stopping the drug. Given these limitations, using the safety follow-up of 28/29 days, although it is twice the period of exposition, is considered reasonable.

It is referred to section 5.5. for more details and further comments regarding the design of the pivotal safety studies, ACTT-2 and KHAA. For RECOVERY, safety information was only available from the online publication.

Paediatric population

Currently, no data are available for COVID-19-affected children who were treated with baricitinib. Safety data are available for paediatric patients treated with baricitinib in 3 clinical trials for other therapeutic indications. These trials are ongoing, and safety data as of 16 September 2020 were provided in the dossier.

Study **JAHV** is being performed in patients with Juvenile idiopathic arthritis.

Study **JAIP** is being performed in patients with Atopic dermatitis.

Study **JAGA** is being performed in patients with type 1 interferonopathies.

From these trials, there were 20 patients aged 10 to less than 18 years in Study JAIP, 13 patients aged 10 to less than 18 years in Study JAHV, and 15 patients aged 10 to less than 18 years in Study JAGA.

CHMP's assessment

Pharmacokinetic data for paediatric patients 10<18 years of age from the three paediatric studies (JAHV, JAIP, JAGA) in other indications are discussed in the pharmacokinetic section. There are more paediatric studies in the clinical programme, being performed in: Systemic juvenile idiopathic arthritis (I4V-MC-JAHU), and in active JIA-associated uveitis or chronic anterior anti-nuclear antibody positive uveitis without systemic features (I4V-MC-JAHW). With their responses to the 1st RSI, the MAH has withdrawn their claim for an indication in children – see Section 5.5.

Patient exposure

Combined exposure ACTT-2 and KHAA

In studies ACTT-2 and KHAA, hospitalised patients received active treatment for a maximum of 14 days, or until hospital discharge, whichever came first. In total:

- 1257 patients received baricitinib (in total 1442 patient-weeks of exposure), and
- 1261 patients received placebo (in total 1465 patient-weeks of exposure).

The majority (~57%) of patients were on study drug for at least 7 days, and a smaller (~20%) proportion of patients was exposed for at least 14 days.

Exposure in ACTT-2 and KHAA separately

In study ACTT-2 there were 1033 patients enrolled, of whom 1016 patients received study drug.

- 507 baricitinib + remdesivir (in total 575.4 patient-weeks of exposure), and
- 509 placebo + remdesivir (in total 574.0 patient-weeks of exposure).

About half (53%) of the patients in ACTT-2 received study drug for at least 7 days, a group of 20% of patients had received study drug for at least 14 days. The range in exposure to study drug was 1-15 days.

In study KHAA there were 1525 patients being randomised, of whom 1502 received study drug.

- 752 placebo + SOC, and
- 750 baricitinib + SOC.

The majority (60%) of patients in KHAA received study drug for at least 7 days, a group of 20% of patients had received study drug for at least 14 days. The range in exposure to study drug was 1-15 days.

Exposure in the clinical programme

Across the entire baricitinib clinical development programme, as of 13 February 2021, approximately 548 healthy volunteers and 12 746 patients have received baricitinib, totalling 13 294 patients. Approximately 120 paediatric patients have received baricitinib. Of them, 61 patients were ≤12 years of age and 62 patients were 12 - 18 years of age. Cumulatively, as of 31 January 2021, it is estimated that approximately 232 500 patients (representing 138 600 patient-years of exposure) have received baricitinib worldwide since 13 February 2017.

Table 38 Study drug exposure in the combined studies ACTT-2 and KHAA.

	PBO (N=1261)	BARI 4-mg (N=1257)
Days of exposure, n (%)		
> 0 day	1261 (100)	1257 (100)
>= 4 days	1083 (85.9)	1094 (87.0)
>= 7 days	731 (58.0)	709 (56.4)
>= 10 days	473 (37.5)	457 (36.4)
>= 14 days	269 (21.3)	243 (19.3)
Days of exposure, n (%)		
> 0 to < 4 days	178 (14.1)	163 (13.0)
>= 4 to < 7 days	352 (27.9)	385 (30.6)
>= 7 to < 10 days	258 (20.5)	252 (20.0)
>= 10 to < 14 days	204 (16.2)	214 (17.0)
>= 14 days	269 (21.3)	243 (19.3)
Patient days of exposure		
Number of patients	1261	1257
Mean	8.1	8.0
SD	4.09	4.05
Minimum	1	1
Q1	5.0	5.0
Median	7.0	7.0
Q3	12.0	12.0
Maximum	15	15
Patient days of study duration		
Number of patients	1261	1257
Mean	25.4	25.9
SD	6.42	6.11
Minimum	1	2
Q1	27.0	28.0
Median	28.0	28.0
Q3	28.0	28.0
Maximum	34	45
Total patient-weeks of exposure [1]	1464.6	1441.6
Total patient-years of exposure [2]	28.07	27.63
Total patient-weeks of study duration [3]	4575.3	4654.9
Total patient-years of study duration [4]	87.69	89.21

Abbreviations: N = number of patients in the analysis population; n = number of patients in the specified category; SD = standard deviation.
PBO and BARI 4-mg groups includes RDV from ACTT-2.
[1] Total patient-weeks of exposure is calculated as sum of duration of exposure in days for all patients in dosing regimen
[2] Total patient-years of exposure is calculated as sum of duration of exposure in days for all patients in dosing regimen / 365.25.
[3] Total patient-weeks of study duration is calculated as sum of duration in the study in days for all patients in dosing regimen/7.
[4] Total patient-years of study duration is calculated as sum of duration in the study in days for all patients in dosing regimen / 365.25.

CHMP's assessment

The patient numbers in both studies, ACTT-2 and KHAA combined, as well as separately, are sufficiently large to also detect uncommon adverse events with sufficient certainty, by roughly relying on the 'rule of three' (Eypasch 1995).

The exposure to the study drug (baricitinib) was similar in both trials. In both ACTT-2 and KHAA, the study drug was administered for 14 days or up to hospital discharge, whichever came first. Accordingly, in both trials, the majority (50%-60%) of patients were on study drug for at least 7 days, and 20% were treated up to 14-15 days. It is considered that this duration of exposure is reasonably representative of treatment of hospitalised patients with Covid-19 who require supplemental oxygen.

The design of study KHAA may reflect current treatment preference better than study ACTT-2. In that study, baricitinib was combined with 'standard-of-care', which usually (80%) was treatment with corticosteroids. Therefore, besides the safety experience in the pooled studies, the safety experience in the separate studies and in patients in KHAA on concomitant corticosteroids deserves attention.

Adverse events

Summary of Adverse Events

In the **pooled** data, TEAEs were reported by 43% of patients in the integrated baricitinib group compared to 46% of patients in the integrated placebo group (Table 39). The frequency of deaths due to an AE was lower (p=0.001) in the integrated baricitinib group (2.8%) compared to the integrated placebo group (5.4%), consistent with the results for all-cause mortality (see Clinical efficacy section). Serious adverse events were reported by a lower proportion (p=0.016) of patients in the integrated baricitinib group (16%) compared to the integrated placebo group (19%). The frequency of permanent study drug discontinuation due to AEs (not including death due to an AE) was lower (p=0.038) in the integrated baricitinib group (6.5%) compared with the integrated placebo group (8.7%). Temporary interruptions due to an AE equally occurred in the baricitinib group (5.9%) and in the placebo group (6.9%).

Table 39 Overview of AEs in the combined studies ACTT-2 and KHAA.

Category	PBO (N=1261) n (%)	PBO (N=1261) IR [PYR]	BARI 4-mg (N=1257) n (%)	BARI 4-mg (N=1257) IR [PYR]
Death due to AE	68 (5.4)	234.2 [29.0]	35 (2.8)	123.8 [28.3]
Serious adverse event	244 (19.3)	869.1 [28.1]	197 (15.7)	713.6 [27.6]
TEAE	576 (45.7)	2490.0 [23.1]	544 (43.3)	2364.9 [23.0]
Permanent discontinuation from study treatment due to adverse event (including death due to AE)	145 (11.5)	515.9 [28.1]	104 (8.3)	378.0 [27.5]
Permanent discontinuation from study treatment due to adverse event (not including death due to AE)	110 (8.7)	394.1 [27.9]	82 (6.5)	297.5 [27.6]
Temporary interruption due to adverse event	87 (6.9)	315.8 [27.6]	74 (5.9)	273.6 [27.0]

Abbreviations: IR = incidence rate; N = number of patients in the analysis population; n = number of patients in the specified category; PYR = patient-years at risk; TEAE = treatment-emergent adverse event.
IR is 100 times the number of patients experiencing the adverse event divided by the event-specific exposure and observation time (exposure and observation time up to the event for patients with the event and to the end of the period for patients without the event, in years).
MedDRA Version 23.0 for ACTT-2 and MedDRA Version 23.1 for KHAA.

In study **ACTT-2**, the proportion of patients with at least one AE was 41.4% in the baricitinib group and 47.5% in the placebo group. Most of the AEs were considered unrelated and severe (grade 4) which occurred in 36% in the baricitinib group and 39% in the placebo group. Life-threatening (grade 4) events occurred in 14% of patients in the baricitinib group versus 23% of patients in the placebo group. Few events were considered related, 4% severe and 1% life-threatening in both treatment groups. In the baricitinib group 4.5% of patients had died, as compared to 7.3% of patients in the placebo group. SAEs occurred in 17.2% of patients in the baricitinib group versus 21.4% of patients in the placebo group. Discontinuations due to an AE (including death) occurred in 7.1% of patients in the baricitinib group versus 11.8% of patients on placebo.

In study **KHAA**, the proportion of patients with at least one AE was 45% in the baricitinib group and 44% in the placebo group. Severity of AEs was uniformly distributed as 17% of patients had mild AEs, 12% had moderate severity AEs, and 16% had severe AEs, similar in the two treatment groups. In the baricitinib group 1.6% of patients had died, as compared to 4.1% in the placebo group. SAEs occurred in 15% of the baricitinib group versus 18% of the placebo group. Discontinuations due to an AE (including death) occurred in 7.5% of patients in the baricitinib group versus 9.3% of patients on placebo.

CHMP's assessment

In the data of studies ACTT-2 and KHAA combined, the occurrence of AEs (43% versus 46%), SAEs (16% versus 19%), deaths 'due to an AE' (2.8% versus 5.4%), discontinuations due to an AE (6.5% versus 8.7%) was overall lower for baricitinib as compared to placebo. That was also seen when assessing the data of studies ACTT-2 and KHAA separately.

It is already noted here that the safety event of death 'due to an AE' is not completely understood. Because, the AEs referred to, quite commonly refer to Covid-19, which is the disease baricitinib aims to treat. This is further discussed in the next section.

In both study ACTT-2 and KHAA, the proportion of patients with at least one AE was lower in the baricitinib group as compared to the placebo group. There was not much difference in absolute occurrence in overall AEs between the trials. This was not expected, as in study ACTT-2 only severe and life-threatening events (grade 3 and 4) were collected, while in KHAA also mild and moderate (grade 1 and 2) AEs were collected. It could be asked for an explanation, but this is not considered to affect the interpretation of the main results (**not pursued**).

Common adverse events

For the **pooled** data, AEs for baricitinib group versus placebo grouped on SOC level occurred in: Investigations 16.6% *versus* 17.5%; Infections and infestations 12.6% *versus* 14.5%; Respiratory, thoracic and mediastinal disorders 12.6% *versus* 15.2%; Vascular disorders 7.3% *versus* 7.8%; Blood and lymphatic system disorders 7.1% *versus* 7.1%; Gastrointestinal disorders 6.7% *versus* 4.8%; Renal and urinary disorders 5.1% *versus* 6.9%; Cardiac disorders 4.1% *versus* 4.3%, Hepatobiliary disorders 1.8% *versus* 1.3%.

Treatment-emergent adverse events at the PT level, occurring in 2% or more of patients in either treatment group are summarised in Table 40. The most frequent events that occurred numerically more often with baricitinib as compared to placebo were: glomerular filtration rate decreased (4.0% *versus* 3.6%) and constipation (2.6 *versus* 1.8%). There was a reversed figure for acute kidney injury (3.7% *versus* 4.7%).

Table 40 AEs reported by ≥2% in any treatment group by preferred term, in the combined studies ACTT-2 and KHAA.

Preferred Term	PBO (N = 1261) n (%)	BARI (N = 1257) n (%)
Hyperglycaemia	63 (5.0)	52 (4.1)
Glomerular filtration rate decreased	45 (3.6)	50 (4.0)
Acute kidney injury	59 (4.7)	46 (3.7)
Anaemia	45 (3.6)	45 (3.6)
Respiratory failure	60 (4.8)	39 (3.1)
Hypotension	34 (2.7)	35 (2.8)
Acute respiratory failure	42 (3.3)	34 (2.7)
Pneumonia	41 (3.3)	33 (2.6)
Constipation	23 (1.8)	33 (2.6)
Haemoglobin decreased	30 (2.4)	31 (2.5)
Lymphocyte count decreased	36 (2.9)	24 (1.9)
Blood glucose increased	30 (2.4)	22 (1.8)
Septic shock	35 (2.8)	21 (1.7)
Lymphopenia	28 (2.2)	12 (1.0)

Abbreviations: ACTT-2 = Adaptive COVID-19 Treatment Trial 2; BARI = baricitinib; N = number of patients in the specified treatment group; n = number of patients reporting at least 1 event; PBO = placebo.

In study **ACTT-2**, among the most common (≥2%) AEs that occurred numerically more frequently in the baricitinib group as compared to placebo were: glomerular filtration decreased (9.7% *versus* 8.3%); deep vein thrombosis (2.4% *versus* 2.0%); hypertension (2.2% *versus* 1.2%). Among the AEs that occurred less frequently in the baricitinib group as compared to placebo were: acute kidney injury (3.9% *versus* 7.1%), AST increased and ALT increased, and respiratory failure, respiratory distress, pneumonia, sepsis.

For study **KHAA**, the most common (≥2%) AEs that occurred numerically more frequently in the baricitinib group as compared to placebo were: constipation (4.4% *versus* 3.1%), hypotension (3.5% *versus* 2.1%), acute kidney injury (3.5% *versus* 3.1%), hyperglycaemia (3.6% *versus* 3.1%), pneumonia (2.8% *versus* 2.7%), anaemia (2.7% *versus* 1.6%), transaminases increased (2.3% *versus* 1.9%), thrombocytosis (2.0% *versus* 0.8%), pulmonary embolism (2.0% *versus* 1.3%). Among the AEs that occurred less frequently in the baricitinib group as compared to placebo were: hypertension, deep venous thrombosis, (acute) respiratory failure, Covid-19 pneumonia, septic shock.

Glomerular filtration rate decreased and 'acute kidney injury' showed numerical differences in opposite directions in the pooled data. There was no difference between baricitinib and placebo in the occurrence of 'creatinine renal clearance decreased' (0.2% *versus* 0.2%, 3 cases each) and a numerically small difference in occurrence of 'haematuria' (0.6% *versus* 0.4%, 7 and 5 cases). 'Renal failure' occurred numerically less frequent in baricitinib as compared to placebo (0.4% *versus* 0.8%, 5 and 10 cases), as was 'renal impairment' (0.2% versus 0.6%, 2 and 7 cases). Nearly all cases of 'glomerular filtration rate decreased' came from study ACTT-2. Cases with acute kidney injury came from both trials: in ACTT-2 the occurrence of acute kidney injury was lower in the baricitinib group as compared to placebo (3.9% *versus* 7.1%); in KHAA this occurrence was numerically similar (3.5% *versus* 3.1%).

Constipation was more frequent with baricitinib than with placebo, in the pooled data (Table 40). The next most frequent AEs in the Gastrointestinal SOC for baricitinib versus placebo were: diarrhoea (1.1% versus 0.9%, 14 and 11 cases); nausea (0.6% versus 0.4%, 8 and 5 cases), and vomiting (0.6% versus 0.4%, 7 and 3 cases). All cases of constipation and diarrhea were from study KHAA.

CHMP's assessment

From the pooled and individual data (not shown) of studies ACTT-2 and KHAA, there appeared to be no new safety signals for baricitinib.

In the pooled data and in the individual trial data, there were no large differences between the two treatment groups in AEs at the SOC level. Of the most common (≥2%) AEs in the pooled data, there only were two that occurred numerically more often with baricitinib as compared to placebo: glomerular filtration rate decreased (4.0% versus 3.6%) and constipation (2.6 versus 1.8%).

Glomerular filtration rate decreased was seen more frequently with baricitinib than with placebo (4.0% versus 3.6%), while there was a reversed figure for acute kidney injury (3.7% versus 4.7%). The differences between baricitinib and placebo in the occurrence of these two renal AEs are small. Other renal AEs in the pooled data (creatinine renal clearance decreased, haematuria, renal failure, renal impairment) did not point to an imbalance that would be unfavourable of baricitinib. The findings in the pooled data are overall supported by the findings in the individual studies. Renal failure or decreased renal function is not a known or potential risk of treatment with baricitinib. Acute kidney injury with suddenly reduced glomerular filtration rate however is a known complication of Covid-19, which may be caused directly by the virus or indirectly through inflammation and immune dysfunction, and/or through dysfunction of other organs [Nadim et al. 2020 *https://www.nature.com/articles/s41581-020-00356-5*]. Consequently, based on the available data, (signs of) renal disorder may not be considered as an ADR of baricitinib.

Constipation and diarrhea both occurred in low numbers, but both more frequently with baricitinib as compared to placebo. Constipation and diarrhea are not known as ADRs for baricitinib. Although diarrhea is an ADR of tofacitinib [Xeljanz SmPC], diarrhea or constipation are currently not listed as ADR for other JAK inhibitors [Jyseleca SmPC, Rinvoq SmPC]. Obstipation is quite a common event in severely ill patients at the ICU, which may be due to immobilisation as well as be a consequence of prolonged sedation [Hay et al. 2020 *https://doi.org/10.1016/j.jcrc.2019.01.004*]. Also, corticosteroids, notably dexamethasone, may cause constipation and diarrhea [Neofordex SmPC]. Diarrhea in patients treated at the ICU usually is not caused by bacteria, and may be caused by medication against obstipation, amongst others. All cases of constipation and diarrhea were from study KHAA, which can be understood as a consequence of only collecting grade 3 and 4 events in ACTT-2 and because of the background medication of corticosteroids. Given the low occurrence and the known association of obstipation and diarrhea with critically ill patients at the ICU and as ADR of dexamethasone, it is not proposed to pursue obstipation and diarrhea as probable ADRs of baricitinib.

In the pooled safety data and at the PT level in the individual trial data of ACTT-2 and KHAA, several AEs can be found that are synonyms of Covid-19, or likely manifestations, sequelae, or complications of Covid-19. In the common AEs of the pooled data this is reflected by: respiratory failure, acute respiratory failure, pneumonia, septic shock, glomerular filtration rate decreased/acute kidney injury. From the pooled data as well as from the data of the two trials individually (not shown), at the PT level there is a tendency that AEs reasonably attributable to Covid-19 occur more frequently in the placebo group as compared with the baricitinib group. This means that there currently is no signal that baricitinib would overall worsen Covid-19, or its complications. This assessment includes the analysis of overall survival (see Clinical efficacy section). An exception could be made for VTE, which is a known complication of Covid-19, as well as an ADR of baricitinib and of dexamethasone.

The occurrence of known ADRs of baricitinib: infections, investigations, and VTE is discussed in the sections below.

Serious adverse events and deaths

Serious Adverse Events

For the **pooled data**, Serious adverse events were reported by a lower (p=0.016) proportion of participants in the baricitinib group (15.7%) compared to the placebo group (19.3%).

The most commonly reported SAEs in the baricitinib group were: Respiratory failure (3.1%) compared to the placebo group (4.3%); Acute respiratory failure, by 2.8% of the baricitinib group and 3.6% of the placebo group; Septic shock, by 1.4% of the baricitinib group and 3.6% of the placebo group. Pulmonary embolism and Deep vein thrombosis were reported as an SAE by 1.4% and 0.4% of patients in the baricitinib group compared to 0.6% and 0.5% of patients in the placebo group. Further discussion of VTE is provided in the next section.

In study **ACTT-2**, Serious adverse events were reported by a lower proportion of participants in the baricitinib + remdesivir group (17.2%) compared to the placebo + remdesivir group (21.4%), (Table 41). The most common SAEs reported in the baricitinib + remdesivir group as compared to the placebo + remdesivir group were: respiratory failure (5.7% *versus* 7.3%) and acute respiratory failure (3.6% *versus* 3.1%). Pulmonary embolism occurred more frequently in the baricitinib group (1.0%, 5 cases) as compared to the placebo group (0.2%, 1 case).

In study **KHAA**, Serious adverse events were reported by a lower proportion of participants in the baricitinib + SOC group (14.7%) compared to the placebo + SOC group (18.0%), (Table 42). The most common SAEs reported in the baricitinib + SOC group as compared to the placebo + SOC group were: Acute respiratory failure (2.3% *versus* 3.9%) and respiratory failure (1.3% *versus* 2.3%), Covid-19 pneumonia (2.8% *versus* 2.7%) and Covid-19 (1.1% *versus* 1.3%), septic shock (1.7% *versus* 3.2%), pneumonia (0.9% *versus* 1.3%), pulmonary embolism (1.6% *versus* 0.9%) and deep vein thrombosis (0.5% *versus* 0.7%), acute kidney injury (0.9% *versus* 1.3%). Pulmonary embolism, pneumonia bacterial (0.7% *versus* 0.4%), and pneumothorax (0.8% *versus* 0.3%) occurred more frequently in the baricitinib treated groups as compared to placebo.

For the **pooled data**, the proportion of patients with related SAEs was slightly higher in the baricitinib group (1.6%) compared to the placebo group (1.2%). Only serious pulmonary embolism (0.6% vs 0.2%, respectively) contributed significantly to the observed difference between the 2 groups (difference $\geq$ 0.4%).

Table 41 Serious Adverse Events occurring in ≥5 patients on PT-level, in study ACTT-2

Preferred Term	PBO + RDV (N = 509) n (%)	BARI + RDV (N = 507) n (%)
Any preferred term	109 (21.4)	87 (17.2)
Respiratory failure	37 (7.3)	29 (5.7)
Acute respiratory failure	16 (3.1)	18 (3.6)
Acute kidney injury	11 (2.2)	5 (1.0)
Acute respiratory distress syndrome	10 (2.0)	4 (0.8)
Respiratory distress	7 (1.4)	7 (1.4)
Septic shock	8 (1.6)	4 (0.8)
Hypotension	5 (1.0)	6 (1.2)
Pneumonia	8 (1.6)	2 (0.4)
Multiple organ dysfunction syndrome	6 (1.2)	1 (0.2)
Sepsis	5 (1.0)	2 (0.4)
Hypoxia	3 (0.6)	3 (0.6)
Pulmonary embolism	1 (0.2)	5 (1.0)
Shock	4 (0.8)	2 (0.4)
Cardiac arrest	3 (0.6)	2 (0.4)
Dyspnoea	4 (0.8)	1 (0.2)
Pneumothorax	4 (0.8)	1 (0.2)
Renal failure	5 (1.0)	0 (-)

Abbreviations: ACTT-2 = NIAID Adaptive COVID-19 Treatment Trial (I4V-MC-K001); BARI + RDV = baricitinib plus remdesivir; COVID-2019 = Coronavirus Disease 2019; N = number of patients in the specified treatment group; n = number of patients reporting at least 1 event; NIAID = National Institute of Allergy and Infectious Diseases; PBO + RDV = placebo plus remdesivir.

Table 42 Serious Adverse Events occurring in ≥5 patients on PT-level, in study KHAA.

Preferred Term	PBO + SOC (N=752) n (%)	BARI + SOC (N=750) n (%)
Subjects with ≥1 SAE	135 (18.0)	110 (14.7)
COVID-19 pneumonia	20 (2.7)	21 (2.8)
Septic shock	24 (3.2)	13 (1.7)
COVID-19	10 (1.3)	8 (1.1)
Pneumonia	10 (1.3)	7 (0.9)
Pneumonia bacterial	3 (0.4)	5 (0.7)
Sepsis	4 (0.5)	3 (0.4)
Pneumonia viral	3 (0.4)	2 (0.3)
Acute respiratory failure	29 (3.9)	17 (2.3)
Respiratory failure	17 (2.3)	10 (1.3)
Pulmonary embolism	7 (0.9)	12 (1.6)
Pneumothorax	2 (0.3)	6 (0.8)
Respiratory distress	4 (0.5)	3 (0.4)
Acute respiratory distress syndrome	3 (0.4)	2 (0.3)
Cardio-respiratory arrest	6 (0.8)	2 (0.3)
Acute kidney injury	10 (1.3)	7 (0.9)
Deep vein thrombosis	5 (0.7)	4 (0.5)
Multiple organ dysfunction syndrome	5 (0.7)	4 (0.5)

Selected by Assessor from Clinical Overview Table 2.5.8.30.

Deaths

In the **pooled data**, the proportion of deaths that were attributed to an AE was lower in the baricitinib group (2.8%) compared with the integrated placebo group (5.4%), see Table 43. A similar difference between baricitinib and placebo was seen for Overall Survival (see Clinical Efficacy section). The most frequent AEs resulting in death reported for the baricitinib group as compared to the placebo group were: Respiratory failure (0.6% *versus* 0.8%), Septic shock (0.6% *versus* 0.6%), and Acute respiratory failure (0.5% *versus* 1.2%).

Table 43 AEs leading to death according to preferred term, in the combined studies ACTT-2 and KHAA.

Reason for Death System Organ Class Preferred Term	PBO (N=1261) n (%)	BARI 4-mg (N=1257) n (%)
Death	137 (10.9)	85 (6.8)
Reason for Death:		
Study Disease	69 (5.5)	50 (4.0)
Adverse Event	68 (5.4)	35 (2.8)
Respiratory, thoracic and mediastinal disorders	35 (2.8)	19 (1.5)
Respiratory failure	10 (0.8)	7 (0.6)
Acute respiratory failure	15 (1.2)	6 (0.5)
Acute respiratory distress syndrome	5 (0.4)	1 (0.1)
Hypoxia	1 (0.1)	1 (0.1)
Pneumonia aspiration	0	1 (0.1)
Pulmonary embolism	1 (0.1)	1 (0.1)
Respiratory arrest	1 (0.1)	1 (0.1)
Respiratory distress	1 (0.1)	1 (0.1)
Pneumothorax	1 (0.1)	0
Infections and infestations	14 (1.1)	8 (0.6)
Septic shock	8 (0.6)	7 (0.6)
Pneumonia	2 (0.2)	1 (0.1)
COVID-19 pneumonia	1 (0.1)	0
Sepsis	2 (0.2)	0
Severe acute respiratory syndrome	1 (0.1)	0
Cardiac disorders	9 (0.7)	5 (0.4)
Cardiac arrest	2 (0.2)	1 (0.1)

Cardio-respiratory arrest	5 (0.4)	1 (0.1)
Cardiopulmonary failure	0	1 (0.1)
Pulseless electrical activity	0	1 (0.1)
Sinus tachycardia	0	1 (0.1)
Cardiogenic shock	1 (0.1)	0
Left ventricular failure	1 (0.1)	0
Gastrointestinal disorders	0	1 (0.1)
Gastrointestinal haemorrhage	0	1 (0.1)
General disorders and administration site conditions	4 (0.3)	1 (0.1)
Multiple organ dysfunction syndrome	4 (0.3)	1 (0.1)
Vascular disorders	2 (0.2)	1 (0.1)
Hypotension	0	1 (0.1)
Shock	1 (0.1)	0
Shock haemorrhagic	1 (0.1)	0
Injury, poisoning and procedural complications	1 (0.1)	0
Subdural haematoma	1 (0.1)	0
Metabolism and nutrition disorders	1 (0.1)	0
Metabolic acidosis	1 (0.1)	0
Nervous system disorders	2 (0.2)	0
Cerebral infarction	1 (0.1)	0
Encephalopathy	1 (0.1)	0

Abbreviations: N = number of subjects in population; n = number of subjects within category.
PBO and BARI 4-mg groups includes RDV from ACTT-2.
System organ class is sorted in decreasing frequency and preferred term in decreasing frequency within system organ class in the BARI 4-mg group.

MedDRA version 23.0 for ACTT-2 and MedDRA version 23.1 for KHAA.

In study **ACTT-2**, in the baricitinib + remdesivir group 23/507 (4.5%) died and in the placebo + remdesivir group 37/509 (7.3%) of patients, (also see Clinical efficacy section). According to the death listings, virtually all deaths were labelled as Covid-19 or one of its complications, with some exceptions in the baricitinib group (sinus tachycardia, gastro-intestinal bleeding, aspiration pneumonia) and the placebo group (encephalopathy, pulmonary embolism, acute subdural hemorrhage).

In study **KHAA**, Day 28 all-cause mortality was 62/764 (8.1%) in the baricitinib + SOC group, versus 100/761 (13.1%) in the placebo + SOC group (also see Clinical efficacy section). Up to day 60, the proportions of deaths were 10.4% in the baricitinib group and 15.3% in the placebo group. According to the listings, virtually all deaths were labelled as Covid-19 or one of its complications, with some exceptions in the baricitinib group (acute abdomen, pulmonary embolism, severe hypotension) and the placebo group (cerebral infarction, acquired phimosis, hospital acquired pneumonia (n=2), bilateral pneumothorax).

CHMP's assessment

In the pooled data, the proportion of patients with at least one SAE was lower in the baricitinib group (16%), as compared to the placebo group (19%); this was also seen in the individual trials ACTT-2 and KHAA. The occurrence of SAEs was higher with baricitinib as compared to placebo for pneumonia bacterial (0.7% versus 0.4%) and pulmonary embolism (1.6% versus 0.9%).

From the mortality due to 'study disease' and 'attributable to AEs', as well as from the death listings (not shown), it appears that most of the deaths in both treatment groups are attributable to Covid-19, which is in line with the SAE results. The more frequent SAEs that occurred in at least 5 subjects were delineated separately for studies ACTT-2 and KHAA. It appears that most SAEs could be attributable to Covid-19, as manifestations (e.g. pneumonia, hypoxia, dyspnoea, respiratory failure), sequelae (e.g. acute respiratory distress syndrome) or complications (e.g. acute kidney failure/renal failure, cardiac arrest, sepsis, shock, multiorgan dysfunction, thrombotic events). In that sense, it is not quite understood that 'Covid-19 pneumonia' and 'Covid-19' are listed as AEs, as these constitute

*the indication (**not pursued**). Overall, the importance is: as shown in both trials, there is currently no suggestion that baricitinib, as an immunosuppressive compound, leads to more SAEs, or a worsening in Covid-19, as compared to placebo.*

However, the occurrence of SAEs was higher with baricitinib as compared to placebo for pneumonia bacterial. Thrombotic events and infections will be discussed in the next section.

In study KHAA a quarter of deaths (43 from 162) was attributed to an AE, the other deaths were directly attributed to Covid-19 ('study disease' in the table). In contrast, in trial ACTT-2 most deaths (50 from 60) were attributed to an AE, but commonly these were descriptors of manifestations or complications of Covid-19. In study KHAA, the ~5% percentage points of difference in survival over the 28-day period, in favour of baricitinib, is maintained up to 60 days.

Adverse Events of Special Interest

Infections

Infections, including serious and opportunistic infections, are an identified risk for baricitinib. Infections (reported in at least 2% patients in either treatment group) and serious infections in the **pooled data** are summarised in Table 44.

Table 44 Most common (≥2%) treatment-emergent infections, in the combined studies ACTT-2 and KHAA.

Preferred Term	PBO (N = 1261) n (%)	BARI (N = 1257) n (%)
Any TE infection	183 (14.5)	159 (12.6)
Pneumonia	41 (3.3)	33 (2.6)
Septic shock	35 (2.8)	21 (1.7)
Any Serious infection	94 (7.5)	76 (6.0)
Septic shock	32 (2.5)	17 (1.4)

Abbreviations: ACTT-2 = Adaptive COVID-19 Treatment Trial 2; BARI = baricitinib; N = number of patients in the specified treatment group; n = number of patients reporting at least 1 event; PBO = placebo; TE = treatment-emergent.

Treatment-emergent infections were reported by less patients in the pooled baricitinib group compared to the integrated placebo group, pneumonia was most frequently reported (Table 44). If Covid-19 pneumonia is excluded, the proportions of patients with ≥1TEAE, pneumonia (unspecified) and pneumonias with an identified agent, were lower for baricitinib as compared to placebo (Table 45).

Table 45 Treatment-emergent pneumonia, in the combined studies ACTT-2 and KHAA.

Preferred Term	PBO (N=1261) N (%)	BARI 4-mg (N=1257) N (%)
Patients with >= 1 TEAE excluding COVID-19 pneumonia	72 (5.7)	56 (4.5)
Pneumonia	41 (3.3)	33 (2.6)
Pneumonia bacterial	19 (1.5)	17 (1.4)
Pneumonia aspiration	3 (0.2)	5 (0.4)
Pneumonia viral	3 (0.2)	2 (0.2)
Organising pneumonia	0	1 (0.1)
Pneumonia staphylococcal	4 (0.3)	0
Pneumonia klebsiella	2 (0.2)	0
Pneumonia escherichia	1 (0.1)	0
Pneumonia pseudomonal	1 (0.1)	0
Pneumonia streptococcal	1 (0.1)	0

Abbreviations: CI = confidence interval; N = number of patients in the analysis population; n = number of patients in the specified category; OR = Mantel-Haenszel odds ratio.
See complete footnote on last page of the output.

Apart from pneumonia alone, the most frequent treatment emergent infectious events that occurred in ≥1% of patients in the pooled as well as individual data of studies ACTT-2 and KHAA (Table 46) were: pneumonia, septic shock, pneumonia bacterial, urinary tract infection, sepsis. Urinary tract infection was more frequent in the baricitinib group as compared to the placebo group (1.3% versus 0.8%) in the pooled trials, and bacterial pneumonia was more frequent in the baricitinib group in trial KHAA but not in ACTT-2 (1.5% versus 1.4%, in the pooled trials).

If all new infectious AE are counted (events/treatment group) in the **pooled** trials, the occurrence was similar in the placebo group as compared to the baricitinib group, with 16% (207/1261) versus 14% (166/1257). If probable Covid-19 related events are excluded (septic shock, sepsis, pneumonia viral, pulmonary sepsis, severe acute respiratory syndrome, but not pneumonia then this comparison becomes 12% (149/1261) versus 11% (139/1257). Accordingly, the proportions of patients with at least 1 new infectious AE not directly related to COVID-19 are: 152 (12.1%) in the placebo treatment group and 135 (10.7%) in the baricitinib treatment group.

In **ACTT-2**, there were 82 new infectious events in the placebo group and 49 in the baricitinib group, if the probable Covid-19-related events were excluded then these numbers become 61 in placebo versus 38 in baricitinib.

In **KHAA**, there were 125 new infectious events in the placebo group and 127 in the baricitinib group, if the probable Covid-19-related events are excluded then these numbers become 88 in placebo versus 101 in baricitinib.

Table 46 ***New Non-COVID Infections Through Day 28, by Decreasing Frequency in Pooled Baricitinib Group Safety Population Study ACTT-2, Study KHAA, and Pooled ACTT-2 and KHAA***

	Pooled ACTT-2 and KHAA				**Study ACTT-2**				**Study KHAA**			
	PBO (N=1261)		**BARI (N=1257)**		**PBO (N=509)**		**BARI (N=507)**		**PBO (N=752)**		**BARI (N=750)**	
	n	*%*	n	*%*	n	*%*	n	*%*	N	*%*	n	*%*
Pneumonia	41	*3.3*	33	*2.6*	21	*4.1*	12	*2.4*	20	*2.7*	21	*2.8*
Septic shock	35	*2.8*	21	*1.7*	10	*2.0*	7	*1.4*	25	*3.3*	14	*1.9*
Pneumonia bacterial	19	*1.5*	17	*1.4*	9	*1.8*	3	*0.6*	10	*1.3*	14	*1.9*
Urinary tract infection	10	*0.8*	16	*1.3*	2	*0.4*	6	*1.2*	8	*1.1*	10	*1.3*
Sepsis	17	*1.3*	12	*1.0*	11	*2.2*	4	*0.8*	6	*0.8*	8	*1.1*
Staphylococcal infection	1	*0.1*	5	*0.4*	1	*0.2*	1	*0.2*	0		4	*0.5*
Bacteraemia	8	*0.6*	4	*0.3*	5	*1.0*	2	*0.4*	3	*0.4*	2	*0.3*
Respiratory tract infection	1	*0.1*	4	*0.3*	0		0		1	*0.1*	4	*0.5*
Candida infection	1	*0.1*	3	*0.2*	0	*0.0*	1	*0.2*	1	*0.1*	2	*0.3*
Oral candidiasis	0		3	*0.2*	0		0		0		3	*0.4*
Staphylococcal bacteraemia	2	*0.2*	3	*0.2*	1	*0.2*	0	*0.0*	1	*0.1*	3	*0.4*
Acute sinusitis	0		2	*0.2*	0		0		0		2	*0.3*
Bacterial infection	6	*0.5*	2	*0.2*	0		0		6	*0.8*	2	*0.3*
Clostridium difficile infection	0		2	*0.2*	0	*0.0*	2	*0.4*	0		0	
Conjunctivitis	1	*0.1*	2	*0.2*	0		0		1	*0.1*	2	*0.3*
Fungal infection	0		2	*0.2*	0	*0.0*	1	*0.2*	0		1	*0.1*
Lower respiratory tract infection	1	*0.1*	2	*0.2*	0	*0.0*	1	*0.2*	1	*0.1*	1	*0.1*
Pneumonia viral	3	*0.2*	2	*0.2*	0		0		3	*0.4*	2	*0.3*
Systemic candida	1	*0.1*	2	*0.2*	1	*0.2*	0	*0.0*	0		2	*0.3*
Urinary tract infection fungal	0		2	*0.2*	0	*0.0*	1	*0.2*	0		1	*0.1*

New Non-COVID Infections Through Day 28, by Decreasing Frequency in Pooled Baricitinib Group Safety Population
Study ACTT-2, Study KHAA, and Pooled ACTT-2 and KHAA - Continued

	Pooled ACTT-2 and KHAA				Study ACTT-2				Study KHAA			
	PBO (N=1261)		BARI (N=1257)		PBO (N=509)		BARI (N=507)		PBO (N=752)		BARI (N=750)	
	n	%	n	%	n	%	n	%	N	%	n	%
Vascular device infection	1	*0.1*	2	*0.2*	1	*0.2*	2	*0.4*	0		0	
Acinetobacter infection	0		1	*0.1*	0		0		0		1	*0.1*
Aspergillus infection	1	*0.1*	1	*0.1*	1	*0.2*	1	*0.2*	0		0	
Bronchopulmonary aspergillosis	1	*0.1*	1	*0.1*	1	*0.2*	1	*0.2*	0		0	
Coinfection	0		1	*0.1*	0		0		0		1	*0.1*
Device related infection	1	*0.1*	1	*0.1*	0		0		1	*0.1*	1	*0.1*
Empyema	0		1	*0.1*	0		0		0		1	*0.1*
Endocarditis staphylococcal	0		1	*0.1*	0		0		0		1	*0.1*
Enterobacter infection	0		1	*0.1*	0		0		0		1	*0.1*
Escherichia bacteraemia	0		1	*0.1*	0		0		0		1	*0.1*
Fungaemia	0		1	*0.1*	0	*0.0*	1	*0.2*	0		0	
Fungal retinitis	0		1	*0.1*	0		0		0		1	*0.1*
Gastroenteritis	0		1	*0.1*	0		0		0		1	*0.1*
Herpes zoster	3	*0.2*	1	*0.1*	0		0		3	*0.4*	1	*0.1*
Infection	2	*0.2*	1	*0.1*	0		0		2	*0.3*	1	*0.1*
Intervertebral discitis	0		1	*0.1*	0	*0.0*	1	*0.2*	0		0	
Klebsiella bacteraemia	0		1	*0.1*	0		0		0		1	*0.1*
Klebsiella infection	2	*0.2*	1	*0.1*	1	*0.2*	0	*0.0*	1	*0.1*	1	*0.1*
Mastoiditis	1	*0.1*	1	*0.1*	1	*0.2*	0	*0.0*	0		1	*0.1*
Oesophageal candidiasis	0		1	*0.1*	0	*0.0*	1	*0.2*	0		0	
Oral herpes	1	*0.1*	1	*0.1*	0		0		1	*0.1*	1	*0.1*
Pharyngitis	0		1	*0.1*	0		0		0		1	*0.1*
Prostatic abscess	0		1	*0.1*	0	*0.0*	1	*0.2*	0		0	
Pulmonary sepsis	0		1	*0.1*	0		0		0		1	*0.1*

New Non-COVID Infections Through Day 28, by Decreasing Frequency in Pooled Baricitinib Group Safety Population
Study ACTT-2, Study KHAA, and Pooled ACTT-2 and KHAA- Continued

	Pooled ACTT-2 and KHAA				Study ACTT-2				Study KHAA			
	PBO (N=1261)		BARI (N=1257)		PBO (N=509)		BARI (N=507)		PBO (N=752)		BARI (N=750)	
	n	%	n	%	n	%	n	%	N	%	n	%
Pulmonary tuberculosis	0		1	*0.1*	0		0		0		1	*0.1*
Respiratory tract infection bacterial	1	*0.1*	1	*0.1*	1	*0.2*	0	*0.0*	0		1	*0.1*
Severe acute respiratory syndrome	3	*0.2*	1	*0.1*	0		0		3	*0.4*	1	*0.1*
Sinusitis	1	*0.1*	1	*0.1*	1	*0.2*	0	*0.0*	0		1	*0.1*
Stenotrophomonas infection	1	*0.1*	1	*0.1*	0		0		1	*0.1*	1	*0.1*
Superinfection bacterial	0		1	*0.1*	0		0		0		1	*0.1*
Tinea cruris	1	*0.1*	1	*0.1*	0		0		1	*0.1*	1	*0.1*
Tinea infection	0		1	*0.1*	0		0		0		1	*0.1*
Tonsillitis	0		1	*0.1*	0		0		0		1	*0.1*
Tracheitis	0		1	*0.1*	0		0		0		1	*0.1*
Urosepsis	1	*0.1*	1	*0.1*	1	*0.2*	0	*0.0*	0		1	*0.1*
Vulvovaginal candidiasis	0		1	*0.2*	0		0		0		1	*0.4*
Abscess	1	*0.1*	0		1	*0.2*	0	*0.0*	0		0	
Bacterial sepsis	2	*0.2*	0		0		0		2	*0.3*	0	
Body tinea	1	*0.1*	0		0		0		1	*0.1*	0	
Candida sepsis	1	*0.1*	0		1	*0.2*	0	*0.0*	0		0	
Cellulitis	1	*0.1*	0		0		0		1	*0.1*	0	
Cystitis	2	*0.2*	0		0		0		2	*0.3*	0	
Device related bacteraemia	1	*0.1*	0		0		0		1	*0.1*	0	
Enterococcal infection	1	*0.1*	0		1	*0.2*	0	*0.0*	0		0	
Eye infection fungal	1	*0.1*	0		0		0		1	*0.1*	0	
Genital herpes	1	*0.1*	0		0		0		1	*0.1*	0	
Haemophilus infection	1	*0.1*	0		0		0		1	*0.1*	0	
Herpes simplex	2	*0.2*	0		0		0		2	*0.3*	0	

New Non-COVID Infections Through Day 28, by Decreasing Frequency in Pooled Baricitinib Group Safety Population
Study ACTT-2, Study KHAA, and Pooled ACTT-2 and KHAA- Continued

	Pooled ACTT-2 and KHAA				Study ACTT-2				Study KHAA			
	PBO (N=1261)		BARI (N=1257)		PBO (N=509)		BARI (N=507)		PBO (N=752)		BARI (N=750)	
	n	%	n	%	n	%	n	%	N	%	n	%
Incision site cellulitis	1	*0.1*	0		0		0		1	*0.1*	0	
Listeriosis	1	*0.1*	0		0		0		1	*0.1*	0	
Lung abscess	1	*0.1*	0		1	*0.2*	0	*0.0*	0		0	
Oral infection	1	*0.1*	0		0		0		1	*0.1*	0	
Oropharyngeal candidiasis	1	*0.1*	0		0		0		1	*0.1*	0	
Pneumonia Escherichia	1	*0.1*	0		1	*0.2*	0	*0.0*	0		0	
Pneumonia klebsiella	2	*0.2*	0		1	*0.2*	0	*0.0*	1	*0.1*	0	
Pneumonia pseudomonal	1	*0.1*	0		0		0		1	*0.1*	0	
Pneumonia staphylococcal	4	*0.3*	0		3	*0.6*	0	*0.0*	1	*0.1*	0	
Pneumonia streptococcal	1	*0.1*	0		1	*0.2*	0	*0.0*	0		0	
Staphylococcal sepsis	1	*0.1*	0		0		0		1	*0.1*	0	
Strongyloidiasis	1	*0.1*	0		0		0		1	*0.1*	0	
Tooth infection	1	*0.1*	0		0		0		1	*0.1*	0	
Upper respiratory tract infection bacterial	2	*0.2*	0		2	*0.4*	0	*0.0*	0		0	
Urinary tract candidiasis	2	*0.2*	0		0		0		2	*0.3*	0	
Urinary tract infection enterococcal	1	*0.1*	0		0		0		1	*0.1*	0	
Varicella zoster virus infection	1	*0.1*	0		0		0		1	*0.1*	0	
Vulvovaginal mycotic infection	1	*0.1*	0		1	*0.2*	0	*0.0*	0		0	

Abbreviations: BARI = baricitinib; N = number of subjects in the analysis population; n = number of subjects in the specified category; PBO = placebo.

The numbers of treatment emergent (non-Covid-19) serious infectious events were 56 events in the integrated baricitinib group compared with 78 events in the integrated placebo group (Table 47). The most common infection SAEs were pneumonia (sic) and septic shock, occurring more frequently in the placebo group. The proportions of patients with at least 1 infectious SAE not directly related to COVID-19 are: 49 (3.9%) in the baricitinib treatment group and 65 (5.2%) in the placebo treatment group.

Table 47 Treatment-emergent serious infections, in the combined studies ACTT-2 and KHAA.

	Pooled ACTT-2 and KHAA				**Study ACTT-2[b]**				**Study KHAA**			
	PBO (N=1261)		**BARI (N=1257)**		**PBO (N=509)**		**BARI (N=507)**		**PBO (N=752)**		**BARI (N=750)**	
	n	*%*	n	*%*	n	*%*	n	*%*	N	*%*	n	*%*
Septic shock	32	*2.5*	17	*1.4*	8	*1.6*	4	*0.8*	24	*3.2*	13	*1.7*
Pneumonia	18	*1.4*	9	*0.7*	8	*1.6*	2	*0.4*	10	*1.3*	7	*0.9*
Pneumonia bacterial	3	*0.2*	5	*0.4*	0		0		3	*0.4*	5	*0.7*
Sepsis	9	*0.7*	5	*0.4*	4	*0.8*	1	*0.2*	4	*0.5*	3	*0.4*
Staphylococcal infection	0		3	*0.2*	0		0		0		3	*0.4*
Pneumonia viral	3	*0.2*	2	*0.2*	0		0		3	*0.4*	2	*0.3*
Staphylococcal bacteraemia	0		2	*0.2*	0		0		0		2	*0.3*
Urinary tract infection	2	*0.2*	2	*0.2*	0	*0.0*	1	*0.2*	2	*0.3*	1	*0.1*
Empyema	0		1	*0.1*	0		0		0		1	*0.1*
Endocarditis staphylococcal	0		1	*0.1*	0		0		0		1	*0.1*
Enterobacter infection	0		1	*0.1*	0		0		0		1	*0.1*
Intervertebral discitis	0		1	*0.1*	0	*0.0*	1	*0.2*	0		0	
Klebsiella bacteraemia	0		1	*0.1*	0		0		0		1	*0.1*
Klebsiella infection	0		1	*0.1*	0		0		0		1	*0.1*
Lower respiratory tract infection	0		1	*0.1*	0	*0.0*	1	*0.2*	0		0	
Prostatic abscess	0		1	*0.1*	0	*0.0*	1	*0.2*	0		0	
Pulmonary sepsis	0		1	*0.1*	0		0		0		1	*0.1*
Severe acute respiratory syndrome	3	*0.2*	1	*0.1*	0		0		3	*0.4*	1	*0.1*
Systemic candida	0		1	*0.1*	0		0		0		1	*0.1*
Aspergillus infection	1	*0.1*	0		1	*0.2*	0		0		0	
Bacteraemia	1	*0.1*	0		0		0		1	*0.1*	0	

	Pooled ACTT-2 and KHAA				Study ACTT-2[a]				Study KHAA			
	PBO (N=1261)		BARI (N=1257)		PBO (N=509)		BARI (N=507)		PBO (N=752)		BARI (N=750)	
	n	%	n	%	n	%	n	%	N	%	n	%
Bacterial infection	1	*0.1*	0		0		0		1	*0.1*	0	
Device related bacteraemia	1	*0.1*	0		0		0		1	*0.1*	0	
Lung abscess	1	*0.1*	0		1	*0.2*	0		0		0	
Pneumonia staphylococcal	1	*0.1*	0		0		0		1	*0.1*	0	
Staphylococcal sepsis	1	*0.1*	0		0		0		1	*0.1*	0	
Urosepsis	1	*0.1*	0		1	*0.2*	0	*00*	0		0	

Abbreviations: BARI = baricitinib; N = number of subjects in the analysis population; n = number of subjects in the specified category; PBO = placebo.

[a] For the integrated safety data, all SAEs were counted if the SAE start date was on or after the treatment start date.

[b] Treatment-emergent serious infections

There was no clinically meaningful difference between the treatment groups in the proportion of patients who reported an opportunistic infection (1.0% versus 0.9%, respectively), see Table 48.

Table 48 Treatment-emergent opportunistic infections, in the combined studies ACTT-2 and KHAA.

Cluster Preferred Term	PBO (N=1261) n (%)	IR [PYR]	BARI 4-mg (N=1257) n (%)	IR [PYR]
TE OI	11 (0.9)	38.92 [28.27]	12 (1.0)	43.32 [27.70]
Candida infection	0	0.00 [28.07]	2 (0.2)	7.24 [27.62]
Systemic candida	1 (0.1)	3.56 [28.11]	2 (0.2)	7.23 [27.66]
Aspergillus infection	1 (0.1)	3.56 [28.07]	1 (0.1)	3.62 [27.62]
Bronchopulmonary aspergillosis	1 (0.1)	3.56 [28.11]	1 (0.1)	3.62 [27.62]
Fungaemia	0	0.00 [28.07]	1 (0.1)	3.62 [27.64]
Fungal retinitis	0	0.00 [28.07]	1 (0.1)	3.62 [27.66]
Herpes zoster	3 (0.2)	10.66 [28.15]	1 (0.1)	3.62 [27.63]
Oesophageal candidiasis	0	0.00 [28.07]	1 (0.1)	3.62 [27.65]
Pulmonary tuberculosis	0	0.00 [28.07]	1 (0.1)	3.62 [27.63]
Urinary tract infection fungal	0	0.00 [28.07]	1 (0.1)	3.62 [27.62]
Candida sepsis	1 (0.1)	3.56 [28.09]	0	0.00 [27.63]
Eye infection fungal	1 (0.1)	3.56 [28.08]	0	0.00 [27.63]
Listeriosis	1 (0.1)	3.56 [28.07]	0	0.00 [27.63]
Oropharyngeal candidiasis	1 (0.1)	3.56 [28.07]	0	0.00 [27.63]
Varicella zoster virus infection	1 (0.1)	3.56 [28.07]	0	0.00 [27.63]

Abbreviations: ATE = arterial thromboembolic event; DVT = deep vein thrombosis; HLT = high level term; IR = incidence rate; MACE = major adverse cardiovascular event; N = number of patients in the analysis population; n = number of patients in the specified category; NMSC = non-melanoma skin cancer; OI = opportunistic infections; OR = Mantel-Haenszel odds ratio; PE = pulmonary embolism; PYR = patient-years at risk; SMQ = Standardised MedDRA Query; TEAE = treatment-emergent adverse event; VTE = venous thromboembolic event.

In studies **ACTT-2 and KHAA** separately, neither infections nor serious infections were reported at higher frequencies in the baricitinib groups of the individual studies. In ACTT-2 there were more serious infectious events in the placebo group than in the baricitinib group (23 versus 12) and also if probable Covid-19 related events were excluded (11 versus 5). In KHAA there were more serious infectious events in the placebo group than in the baricitinib group (54 versus 44), but not when probable Covid-19 related events (defined above) were excluded (20 versus 24).

CHMP's assessment

Infections, including serious and opportunistic infections, are an identified risk for baricitinib.

From the pooled data of studies ACTT-2 and KHAA it appears that infections and serious infections occurred less frequently with baricitinib as compared to placebo, and opportunistic infections were not more frequent with baricitinib. It preliminary seems that the occurrence of new (non-SARS-CoV-2) infections also is lower in the baricitinib group as compared to the placebo group, the proportions of patients with at least 1 new treatment emergent non-Covid-19 infection (excluding probable manifestation, sequels or complications of Covid-19) was clarified by the MAH. The attribution of infections was however not further revised, it must therefore be assumed that this is the best attainable result. As concluded in previous round, the difference between baricitinib and placebo is considered small, and overall there is no indication that baricitinib would lead to more new (non-Covid-19) infectious events. The issue therefore is ***not pursued*** *but the proposed text for the* ***SmPC*** *should be revised: 'In COVID-19 placebo-controlled studies, the proportion of patients with non-Covid19 infections ~~in patients~~ treated with baricitinib was 10.7~~12.6~~% compared to 12.1~~14.5~~% in the placebo group.'*

According to the AEs at the PT level within the Infections and infestations SOC (Table 46) in the pooled data, the SOC still contains a mix of infection AEs that: are synonymous to the indication (severe acute respiratory syndrome); maybe synonymous to the indication (respiratory tract infection, lower

respiratory tract infection, pneumonia viral) or maybe a complication of it (septic shock, sepsis); form a remaining group of new infections presumably not due to SARS-CoV-2. If the AEs that certainly or probably cover Covid-19 (indicated above) are all subtracted from the overall infection AEs, it preliminary seems that the occurrence of new (non-Covid-19) infections is still lower in the baricitinib group as compared to the placebo group (11% versus 12%).

The results for infections, opportunistic infections, and serious infections in the individual studies were basically in line with the pooled results, with the exception in KHAA the occurrence of serious infections was somewhat higher with baricitinib as compared to placebo.

Venous Thromboembolic Events

The VTE events of Pulmonary embolism (PE) and Deep venous thrombosis (DVT) are ADRs of baricitinib treatment and VTE is an important potential risk for baricitinib.

In the analysis of the **pooled data**, treatment-emergent VTEs were reported by 3.3% of patients treated with baricitinib and by 2.8% of patients treated with placebo (Table 49).

Pulmonary embolism was reported by 18 patients (1.4%) in the integrated baricitinib group and 11 patients (0.9%) in the integrated placebo group. Fatal events of PE were reported for 1 patient (0.1%) in each of the baricitinib and placebo groups.

Deep vein thrombosis was reported by 19 (1.5%) in the integrated baricitinib group and 16 (1.3%) patients in the integrated placebo group.

Other peripheral venous thrombosis events were reported in the baricitinib treated group by 10 patients (0.8%) and by 11 patients (0.9%) in the placebo group.

Table 49 Treatment-emergent VTE, in the combined studies ACTT-2 and KHAA.

Cluster Preferred Term	PBO (N=1261) n (%)	IR [PYR]	BARI 4-mg (N=1257) n (%)	IR [PYR]
TE VTE	35 (2.8)	123.73 [28.29]	41 (3.3)	147.71 [27.76]
DVT and Other Peripheral Venous Thrombosis	25 (2.0)	88.85 [28.14]	28 (2.2)	101.28 [27.65]
DVT	16 (1.3)	57.01 [28.07]	19 (1.5)	68.72 [27.65]
PE	11 (0.9)	38.98 [28.22]	18 (1.4)	64.72 [27.81]
Other Peripheral Venous Thrombosis	11 (0.9)	39.03 [28.18]	10 (0.8)	36.20 [27.63]

Abbreviations: ATE = arterial thromboembolic event; DVT = deep vein thrombosis; HLT = high level term; IR = incidence rate; MACE = major adverse cardiovascular event; N = number of patients in the analysis population; n = number of patients in the specified category; NMSC = non-melanoma skin cancer; OI = opportunistic infections; OR = Mantel-Haenszel odds ratio; PE = pulmonary embolism; PYR = patient-years at risk; SMQ = Standardised MedDRA Query; TEAE = treatment-emergent adverse event; VTE = venous thromboembolic event.

The overall prevalence of VTE in these studies, that is 3.0% (76 patients with one or more VTE events for the total safety population of 2518 patients), regardless of treatment group, is lower than that reported in the literature for patients hospitalised with COVID-19. Porfidia et al. (2020) estimated the overall incidence of VTE in 3487 patients as 26% (95% CI, 6% to 66%); and Di Minno et al. (2020) estimated the incidence of VTE in the hospitalised population as 32.7% (95% CI, 21.9% to 45.7%), when prophylaxis was used, the incidence decreased to 23.9% (95%CI, 15.9% to 34.4%) (Di Minno et al. 2020).

In the separate studies **ACTT-2 and KHAA**: Treatment-emergent VTE were reported by 4.1% of patients treated with baricitinib + remdesivir and by 3.1% of those treated with placebo + remdesivir in ACTT-2. In Study KHAA, positively-adjudicated VTE AEs were reported by 2.7% of patients treated with

baricitinib + SOC and 2.5% of patients treated with placebo + SOC. In both studies ACTT-2 and KHAA, PE was more frequent in the baricitinib groups as compared to the placebo groups.

In both Study ACTT-2 and Study KHAA, **VTE prophylaxis** was recommended for all patients unless there was a major contraindication for it.

In Study **ACTT-2**, anticoagulant medications were used by 97.6% of patients treated with baricitinib + remdesivir and by 97.8% of those treated with placebo + remdesivir. Data were not collected on dose of anticoagulant medication. About 80% of patients in both treatment groups used anticoagulants prior to enrolment. Prescription *after* enrolment *not* due to an AE was verified in 19.1% of patients in the baricitinib + remdesivir group and in 16.5% of those in the placebo + remdesivir group. Prescription on or after enrolment *due to* an AE was 0% in the baricitinib + remdesivir group and counted as 0.4% of those in the placebo + remdesivir group. The most used agent was enoxaparin in both groups prior to enrolment (63%), and on/after enrolment (16%).

In Study **KHAA**, the proportion of patients in study KHAA who used anti-coagulants was 94% in both treatment groups. The two most frequently reported medications reported that could be used as prophylaxis for VTE were: enoxaparin (74.6% of patients in the baricitinib + SOC group and 71.5% in the placebo + SOC group), heparin (13.9% of patients in the baricitinib + SOC group and 15.6% in the placebo + SOC group). Apixaban, rivaroxaban, dalteparin were used in 1.2% - 5.8% of patients, evenly distributed over treatment groups.

CHMP's assessment

Pulmonary embolism (PE) and Deep venous thrombosis (DVT) are ADRs of baricitinib treatment, and VTE is an important potential risk for baricitinib.

In the trials, VTE was more frequent with baricitinib as compared to placebo. This was mainly due to a numerically higher occurrence of pulmonary embolism. For the data and discussion of haematological changes, it is referred to the section on Laboratory findings.

Covid-19 itself is associated with thrombotic complications, including DVT and PE [Malas 2021 https://doi.org/10.1016/j.eclinm.2020.100639]. Interestingly, the overall occurrence of VTE in the two studies ACTT-2 and KHAA is remarkably lower, as has been observed previously. Even with low numbers, the occurrence of PE was higher in patients treated with baricitinib, in both studies. The occurrence of DVT was only slightly higher in the baricitinib group. In both studies, nearly all patients used prophylactic anti-coagulant treatment. Therefore, it is unlikely that the cases of VTE would be explained by a lack of prophylactic treatment. For treatment with baricitinib, it is proposed that 'Venous Thromboembolism (VTE) prophylaxis is recommended unless contraindicated' in sections 4.2 and 4.4 in the SmPC, which is agreed. The occurrence of DVT (PE and VTE) in patients with Covid-19 is separately mentioned in section 4.8 of the SmPC, which also is agreed.

Arterial Thrombotic Events

Few arterial thrombotic events occurred (Table 50); all AT events were reported in study KHAA.

Table 50 Treatment-emergent AT, in the combined studies ACTT-2 and KHAA.

Cluster Preferred Term	PBO (N=1261) n (%)	IR [PYR]	BARI 4-mg (N=1257) n (%)	IR [PYR]
TE ATE	1 (0.1)	3.57 [28.04]	2 (0.2)	7.25 [27.59]
Peripheral artery occlusion	0	0.00 [28.07]	1 (0.1)	3.62 [27.62]
Peripheral artery thrombosis	0	0.00 [28.07]	1 (0.1)	3.62 [27.60]
Arterial thrombosis	1 (0.1)	3.57 [28.04]	0	0.00 [27.63]

Abbreviations: ATE = arterial thromboembolic event; DVT = deep vein thrombosis; HLT = high level term; IR = incidence rate; MACE = major adverse cardiovascular event; N = number of patients in the analysis population; n = number of patients in the specified category; NMSC = non-melanoma skin cancer; OI = opportunistic infections; OR = Mantel-Haenszel odds ratio; PE = pulmonary embolism; PYR = patient-years at risk; SMQ = Standardized MedDRA Query; TEAE = treatment-emergent adverse event; VTE = venous thromboembolic event.

CHMP's assessment

It does not appear that ATE are more common in baricitinib versus placebo-treated patients. JAK inhibition, as well as the pathological process of Covid-19 may interfere with blood coagulation. Therefore, there is a priori reason to consider venous as well as arterial thrombotic events in the safety assessment. According to the safety data, arterial thrombotic events were few (3 in total) and occurred in both treatment groups. All events occurred in trial KHAA; it may be that such events were not reported in ACTT-2 as in that trial AEs of grade 1 or 2 were not collected. It is referred to the sections on MACE and on investigations for further discussion.

Major adverse cardiovascular events

The **pooled analyses** for MACE showed that 12 patients (1.0%) in the integrated baricitinib group presented with one or more MACE events in comparison to 15 patients (1.2%) in the placebo group (Table 51). Cardiac disorders leading to death occurred less in the baricitinib group (0.4%, 5 patients) as compared to placebo (0.8%, 10 patients), without a clear pattern in baricitinib treated patients (Table 43). Cardiac arrest/cardio-respiratory arrest as common (>5%) serious adverse event was more frequent in the placebo group as compared to the baricitinib group, in both studies (Table 41 and Table 42).

Table 51 Treatment-emergent MACE, in the combined studies ACTT-2 and KHAA

Cluster Preferred Term	PBO (N=1261) n (%)	IR [PYR]	BARI 4-mg (N=1257) n (%)	IR [PYR]
MACE	15 (1.2)	52.93 [28.34]	12 (1.0)	43.17 [27.80]
Cardiovascular death	10 (0.8)	35.44 [28.22]	5 (0.4)	18.03 [27.73]
Myocardial Infarction	3 (0.2)	10.69 [28.07]	4 (0.3)	14.48 [27.62]
Stroke	4 (0.3)	14.17 [28.23]	4 (0.3)	14.44 [27.70]

Abbreviations: ATE = arterial thromboembolic event; DVT = deep vein thrombosis; HLT = high level term; IR = incidence rate; MACE = major adverse cardiovascular event; N = number of patients in the analysis population; n = number of patients in the specified category; NMSC = non-melanoma skin cancer; OI = opportunistic infections; OR = Mantel-Haenszel odds ratio; PE = pulmonary embolism; PYR = patient-years at risk; SMQ = Standardized MedDRA Query; TEAE = treatment-emergent adverse event; VTE = venous thromboembolic event.

In study **ACTT-2** the occurrence of MACE was similar in the two treatment groups (8 patients each). In study **KHAA**, MACE was less frequent in baricitinib as compared to placebo treated patients (4 versus 7).

In the **pooled data**, the occurrence of cardiac events (SOC) was similar in the baricitinib group as compared to the placebo group (4.1% *versus* 4.3%), see Table 52.

Table 52 Treatment-emergent cardiac disorders, in the combined studies ACTT-2 and KHAA

System Organ Class Preferred Term	PBO (N=1261) n (%)	IR [PYR]	BARI 4-mg (N=1257) n (%)	IR [PYR]
Cardiac disorders	54 (4.3)	191.75 [28.16]	51 (4.1)	184.40 [27.66]
Atrial fibrillation	17 (1.3)	60.57 [28.07]	8 (0.6)	28.94 [27.64]
Tachycardia	2 (0.2)	7.12 [28.07]	7 (0.6)	25.28 [27.69]
Sinus bradycardia	3 (0.2)	10.68 [28.10]	6 (0.5)	21.80 [27.53]
Bradycardia	6 (0.5)	21.45 [27.98]	5 (0.4)	18.16 [27.53]
Cardio-respiratory arrest	7 (0.6)	24.86 [28.16]	3 (0.2)	10.83 [27.71]
Pulseless electrical activity	1 (0.1)	3.56 [28.07]	3 (0.2)	10.87 [27.60]
Supraventricular tachycardia	1 (0.1)	3.56 [28.07]	3 (0.2)	10.87 [27.60]
Acute myocardial infarction	2 (0.2)	7.12 [28.07]	2 (0.2)	7.24 [27.62]
Arrhythmia	2 (0.2)	7.11 [28.13]	2 (0.2)	7.24 [27.61]
Atrial flutter	0	0.00 [28.07]	2 (0.2)	7.24 [27.61]
Cardiac arrest	6 (0.5)	21.36 [28.08]	2 (0.2)	7.23 [27.65]
Cardiac failure	0	0.00 [28.07]	2 (0.2)	7.22 [27.69]
Cardiopulmonary failure	1 (0.1)	3.56 [28.07]	2 (0.2)	7.24 [27.64]
Sinus tachycardia	1 (0.1)	3.56 [28.08]	2 (0.2)	7.24 [27.63]
Acute left ventricular failure	0	0.00 [28.07]	1 (0.1)	3.62 [27.61]
Angina pectoris	0	0.00 [28.07]	1 (0.1)	3.62 [27.63]
Bundle branch block right	0	0.00 [28.07]	1 (0.1)	3.61 [27.69]
Myocardial infarction	0	0.00 [28.07]	1 (0.1)	3.62 [27.63]
Myocardial ischaemia	1 (0.1)	3.56 [28.07]	1 (0.1)	3.62 [27.61]
Palpitations	1 (0.1)	3.56 [28.13]	1 (0.1)	3.62 [27.65]
Pericardial effusion	0	0.00 [28.07]	1 (0.1)	3.62 [27.64]
Sinus node dysfunction	0	0.00 [28.07]	1 (0.1)	3.62 [27.66]
Tachyarrhythmia	0	0.00 [28.07]	1 (0.1)	3.62 [27.60]
Ventricular tachycardia	3 (0.2)	10.71 [28.01]	1 (0.1)	3.62 [27.65]
Acute coronary syndrome	1 (0.1)	3.56 [28.07]	0	0.00 [27.63]
Aortic valve stenosis	1 (0.1)	3.56 [28.07]	0	0.00 [27.63]
Atrioventricular block	1 (0.1)	3.56 [28.08]	0	0.00 [27.63]
Cardiogenic shock	1 (0.1)	3.56 [28.08]	0	0.00 [27.63]
Coronary artery thrombosis	1 (0.1)	3.56 [28.07]	0	0.00 [27.63]
Left ventricular failure	1 (0.1)	3.56 [28.07]	0	0.00 [27.63]
Myocarditis	1 (0.1)	3.56 [28.06]	0	0.00 [27.63]
Right ventricular dysfunction	1 (0.1)	3.56 [28.10]	0	0.00 [27.63]

Abbreviations: IR = incidence rate; N = number of patients in the analysis population; n = number of patients in the specified category; OR = Mantel-Haenszel odds ratio; PYR = patient-years at risk; TEAE = treatment-emergent adverse event.
See complete footnote on last page of the output.

CHMP's assessment

It does not appear that MACE was more common in baricitinib treated patients as compared to placebo-treated patients. Also, cardiac disorders (SOC) were not more frequent in baricitinib as compared to placebo. Severe COVID-19 infection itself, however, is associated with myocardial damage and cardiac arrhythmia, and cardiac disorder may also be secondary to acute lung injury leading to increased cardiac workload [ESC Guidance, *www.escardio.org/Education/COVID-19-and-Cardiology*].

Hepatic events

ALT and AST ≥3 × ULN are both known ADRs of baricitinib, and the potential for drug-induced liver injury is included in the RMP as an Important potential risk.

Abnormal postbaseline elevations in hepatic laboratory tests in the **pooled data** are summarised in Table 53. Clinically meaningful changes in hepatic enzymes were reported for:

- ALT ≥3 × ULN: 219 (18.0%) baricitinib versus 189 (15.6%) placebo (p=0.118), and
- AST ≥3 × ULN: 140 (11.5%) baricitinib versus 110 (9.1%) placebo (p=0.055)

This is consistent with the findings of abnormal laboratory values (Table 53), which were:

- High alanine aminotransferase (ALT): 369 (50.8%) baricitinib versus 340 (46.8%) placebo (p=0.090), and
- High aspartate aminotransferase (AST): 296 (47.8%) baricitinib versus 270 (44.3%) placebo (p=0.230)

The occurrence of adverse hepatic events in the Hepatobiliary disorders System Organ Class for the two treatment groups was:

- TEAEs occurred in 1.8% of the integrated baricitinib group versus 1.3% in the integrated placebo group (Table 54).
- SAEs occurred in 0% in the integrated baricitinib group versus 0.2% in the integrated placebo group, and there were no hepatobiliary disorders that have led to death in the studies (Table 54).

Table 53 Treatment-emergent elevations in hepatic laboratory tests, in the combined studies ACTT-2 and KHAA.

Analyte Post-Baseline Category Baseline Category	PBO (N=1261) N-obs n (%)	BARI 4-mg (N=1257) N-obs n (%)
SERUM Alanine Aminotransferase		
>=3x ULN at any time post-baseline		
All	1211 189 (15.6)	1219 219 (18.0)
>=5x ULN at any time post-baseline		
All	1211 67 (5.5)	1219 71 (5.8)
>=10x ULN at any time post-baseline		
All	1211 16 (1.3)	1219 21 (1.7)
SERUM Aspartate Aminotransferase		
>=3x ULN at any time post-baseline		
All	1206 110 (9.1)	1218 140 (11.5)
>=5x ULN at any time post-baseline		
All	1206 43 (3.6)	1218 48 (3.9)
>=10x ULN at any time post-baseline		
All	1206 16 (1.3)	1218 16 (1.3)
SERUM Bilirubin		
>=2x ULN at any time post-baseline		
All	1210 44 (3.6)	1218 34 (2.8)

Abbreviations: N = number of patients in the safety analysis set; n = number of patients who have at least one measure falling into both the baseline and post-baseline categories; N-obs = number of patients in the baseline category and have at least one post-baseline measurement; ULN = upper limit of normal; OR = Mantel-Haenszel odds ratio; CI = Confidence Interval.
PBO and BARI 4-mg groups includes RDV from ACTT-2.
Percentages are n divided by N-obs. The 'All' category includes all patients with at least one post-baseline measurement including those patients who have missing baseline.
(a) Mantel-Haenszel odds ratio stratified by study and 95% CI (CI calculated if >=4 events in numerator and >=1 in denominator). Comparator is denominator.
(b) P-value from Cochran-Mantel-Haenszel (CMH) test of general association stratified by study.
(c) Heterogeneity of odds ratios across studies assessed using the Breslow Day test with significant p-value <= 0.10 denoted by 'c'.

Table 54 Treatment-emergent hepatobiliary disorders at the PT level, in the combined studies ACTT-2 and KHAA

System Organ Class Preferred Term	PBO (N=1261) n (%)	IR [PYR]	BARI 4-mg (N=1257) n (%)	IR [PYR]
Hepatobiliary disorders	16 (1.3)	56.93 [28.11]	22 (1.8)	79.97 [27.51]
Hepatic function abnormal	9 (0.7)	32.11 [28.03]	9 (0.7)	32.55 [27.65]
Hyperbilirubinaemia	1 (0.1)	3.56 [28.07]	4 (0.3)	14.51 [27.56]
Hepatic failure	0	0.00 [28.07]	2 (0.2)	7.25 [27.60]
Hepatotoxicity	0	0.00 [28.07]	2 (0.2)	7.24 [27.62]
Cholecystitis acute	0	0.00 [28.07]	1 (0.1)	3.62 [27.64]
Cholelithiasis	0	0.00 [28.07]	1 (0.1)	3.62 [27.62]
Hepatomegaly	0	0.00 [28.07]	1 (0.1)	3.62 [27.61]
Hypertransaminasaemia	0	0.00 [28.07]	1 (0.1)	3.62 [27.62]
Liver injury	2 (0.2)	7.12 [28.09]	1 (0.1)	3.62 [27.61]
Steatohepatitis	0	0.00 [28.07]	1 (0.1)	3.62 [27.62]
Cholestasis	1 (0.1)	3.56 [28.08]	0	0.00 [27.63]
Gallbladder polyp	1 (0.1)	3.56 [28.06]	0	0.00 [27.63]
Hepatic haemorrhage	1 (0.1)	3.56 [28.13]	0	0.00 [27.63]
Hepatic steatosis	1 (0.1)	3.56 [28.06]	0	0.00 [27.63]
Hepatitis	2 (0.2)	7.12 [28.07]	0	0.00 [27.63]
Hepatosplenomegaly	1 (0.1)	3.56 [28.06]	0	0.00 [27.63]

Abbreviations: IR = incidence rate; N = number of patients in the analysis population; n = number of patients in the specified category; OR = Mantel-Haenszel odds ratio; PYR = patient-years at risk; TEAE = treatment-emergent adverse event.

The results regarding abnormal hepatic tests and regarding hepatic adverse events in the individual studies **ACTT-2 and KHAA** (not shown) were in line with the pooled data.

CHMP's assessment

ALT and AST ≥3 × ULN are both known ADRs of baricitinib, and the potential for drug-induced liver injury is included in the RMP as an Important potential risk.

Increases in hepatic laboratory values for ALT and AST occurred more frequently in the baricitinib group as compared to the placebo group. However, hepatic adverse events or serious adverse events did not occur more frequently in the baricitinib group versus the placebo group. This is in line with increases in ALT and AST as known ADRs. The occurrence of high ALT and high AST in the Covid-19 trials was much higher in both treatment groups as compared to the trials in Rheumatoid arthritis and in Atopic dermatitis. Although the precise influence of COVID-19 on the liver remains unclear, abnormalities in liver biochemistries are common in patients with COVID-19, occurring in approximately 15–65% of SARS-CoV-2-infected individuals [Marjot 2021, *https://doi.org/10.1038/s41575-021-00426-4*]. It is therefore agreed that the elevations in liver enzymes in the Covid-19 population are separately described in section 4.8 of the SmPC, and that in the ADR table, reference is made to the differing occurrence of increases in ALT and AST in Covid-19.

Renal events

Nearly all cases of 'glomerular filtration rate decreased' came from study ACTT-2, and cases with acute kidney injury came from both trials (see the section on common Adverse events).

In study **ACTT-2**, 'glomerular filtration decreased' occurred in 10% of patients in the baricitinib group and in 8% of patients of the placebo group (Table 55). Acute kidney injury had occurred in 4% of the baricitinib group and 7% of the placebo group. Renal failure occurred in 6 patients on placebo and did not occur in the baricitinib group.

Table 55 Treatment-emergent renal and urinary disorders at the PT level, in study ACTT-2

Preferred Term	Baricitinib + RDV (N=507)			Placebo + RDV (N=509)		
	n	%	Events	n	%	Events
Any treatment-emergent renal adverse event	76	15	86	89	17	101
Glomerular filtration rate decreased	49	10	51	42	8	43
Acute kidney injury	20	4	21	36	7	39
Blood creatinine increased	10	2	10	9	2	9
Creatinine renal clearance decreased	3	1	4	3	1	3
Renal failure	-	-	-	6	1	6
Azotaemia	-	-	-	1	<1	1

N = Number of subjects in the As Treated Population (number of subjects at risk).
n = Number of subjects reporting event.
Events = Total frequency of events reported.

In study **KHAA**, 'glomerular filtration decreased' within the Investigation SOC occurred in 1 patient in the baricitinib group and in 3 patients of the placebo group. Acute kidney injury had occurred in 3.5% of the baricitinib group and 3.1% of the placebo group (Table 56). Renal failure/renal impairment occurred in 1% of patients on baricitinib and in 1.1% of patients on placebo.

Table 56 Treatment-emergent renal and urinary disorders at the PT level, in study KHAA

System Organ Class Preferred Term	Placebo (N=752) n (%)	Baricitinib-4mg-QD (N=750) n (%)
Renal and urinary disorders	40 (5.3)	42 (5.6)
Acute kidney injury	23 (3.1)	26 (3.5)
Haematuria	4 (0.5)	7 (0.9)
Renal failure	4 (0.5)	5 (0.7)
Renal impairment	7 (0.9)	2 (0.3)
Dysuria	1 (0.1)	1 (0.1)
Renal cyst	0	2 (0.3)
Urinary incontinence	0	2 (0.3)
Leukocyturia	0	1 (0.1)
Oliguria	1 (0.1)	0
Polyuria	0	1 (0.1)
Proteinuria	1 (0.1)	0
Renal mass	1 (0.1)	0
Urinary tract obstruction	0	1 (0.1)

Abbreviations: TEAE = Treatment-Emergent Adverse Event; N = number of subjects in the analysis population; n = number of subjects in the specified category.

CHMP's assessment

In studies ACTT-2 and KHAA, there was no evidence that renal dysfunction, acute kidney injury or other renal disorder, occurred more frequently with baricitinib as compared to placebo.

Patients with suspected or confirmed COVID-19 may present with acute kidney injury as part of their overall illness. It remains unclear if acute kidney injury is largely due to hemodynamic changes and cytokine release or if the virus also leads to direct cytotoxicity. [Nadim 2020, https://www.nature.com/articles/s41581-020-00356-5]. Glomerular dysfunction occurred in ~10% of all patients in KHAA. However, in the pooled data, nearly all cases of GFR decreased stemmed from study ACTT-2, which might be attributed to remdesivir as background treatment. Renal toxicity cannot be excluded for remdesivir [Veklury SmPC].

Laboratory findings

In ACTT-2, laboratory examinations were performed locally at each study site; therefore, the reference LLN and ULN will vary according to local standards. The ranges of laboratory reference values were included in the dossier.

Haematology

Thrombocytosis > 600 x 10^9 cells/L and Neutropenia < 1 x 10^9 cells/L are known ADRs of baricitinib.

The haematologic changes of the **pooled data** are shown in Table 57. Clinically meaningful haematologic changes were reported for:

- Low neutrophils: 79 (7.4%) baricitinib versus 49 (4.6%) placebo (p=0.008), and
- High platelets: 510 (45.5%) baricitinib versus 398 (35.3%) placebo (p=0.001)

This is consistent with findings of neutropenia and thrombocytosis in shift tables:

- Neutropenia <1000 cells/mm3: 26 (2.2%) baricitinib versus 22 (1.9%) placebo (p=0.542), and
- Thrombocytosis >600 000 cells/mm3: 57 (8.2%) baricitinib versus 30 (4.3%) placebo (p=0.004).

The haematological changes in studies **ACTT-2 and KHAA** were consistent with the results of the pooled data.

Hepatology

Changes in hepatic enzymes are presented in the section on AESI's, above.

Chemistry

Chemistry changes in the **pooled data** are summarised in Table 57. Creatine phosphokinase evaluation was not available for Study ACTT-2, however laboratory values were collected in KHAA. Creatine phosphokinase analysis in Study KHAA showed no differences between the baricitinib + SOC treatment group and the placebo + SOC group (for 3.7% versus 3.3% of patients CPK >5 × ULN was reported, respectively).

Table 57 Treatment-emergent high/low laboratory analytes, in the combined studies ACTT-2 and KHAA

Category Analyte Criterion	PBO (N=1261) NAR n (%)	BARI 4-mg (N=1257) NAR n (%)
Chemistry		
Alanine Aminotransferase		
Low	1158 14 (1.2)	1161 9 (0.8)
High	727 340 (46.8)	726 369 (50.8)
Aspartate Aminotransferase		
Low	1175 20 (1.7)	1175 25 (2.1)
High	609 270 (44.3)	619 296 (47.8)
Bilirubin		
Low	1115 75 (6.7)	1105 84 (7.6)
High	1124 116 (10.3)	1116 82 (7.3)
Creatinine		
Low	933 277 (29.7)	929 240 (25.8)
High	1095 143 (13.1)	1107 112 (10.1)
C Reactive Protein		
Low	1108 2 (0.2)	1124 1 (0.1)
High	39 17 (43.6)	28 13 (46.4)
Glucose		
Low	1176 13 (1.1)	1173 12 (1.0)
High	777 211 (27.2)	728 164 (22.5)
Hematology		
Basophils		
Low	1067 17 (1.6)	1065 16 (1.5)
High	1061 62 (5.8)	1069 38 (3.6)
Eosinophils		
Low	1013 12 (1.2)	1011 10 (1.0)
High	1068 88 (8.2)	1068 93 (8.7)
Hemoglobin		
Low	868 346 (39.9)	882 313 (35.5)
High	1188 22 (1.9)	1180 17 (1.4)
Lymphocytes		
Low	619 161 (26.0)	566 112 (19.8)
High	1104 47 (4.3)	1101 66 (6.0)
Monocytes		
Low	1089 24 (2.2)	1081 34 (3.1)
High	998 359 (36.0)	997 341 (34.2)
Neutrophils		
Low	1056 49 (4.6)	1069 79 (7.4)
High	704 285 (40.5)	679 277 (40.8)
Platelets		
Low	1038 87 (8.4)	1030 66 (6.4)
High	1126 398 (35.3)	1120 510 (45.5)
Leukocytes		
Low	1049 92 (8.8)	1071 119 (11.1)
High	959 355 (37.0)	940 340 (36.2)

Abbreviations: N = number of patients in the analysis population; n = number of patients with the specified abnormality; NAR = Number of patients at risk for the specified abnormality in each treatment group; OR = Mantel-Haenszel odds ratio; CI = Confidence Interval. PBO and BARI 4-mg groups includes RDV from ACTT-2.

CHMP's assessment

Thrombocytosis, neutropenia, hypercholesterolaemia and hypertriglyceridemia, ALT and AST increased, creatine phosphokinase increased > 5x ULN, are ADRs of baricitinib. Thrombocytosis, neutropenia, ALT and AST increased were confirmed to be ADRs in the trials ACTT-2 and KHAA. There were no signals for other laboratory analytes to be considered as new ADR.

Because the frequency of occurrence differed in patients with Covid-19 as compared to patients with Rheumatoid arthritis and Atopic dermatitis, for the ADR table in section 4.8, it is proposed to change the frequency in Covid-19 accordingly: *In patients treated with baricitinib in COVID-19 clinical trials, ALT ≥3 x ULN, AST ≥ 3 x ULN were very common; PE, DVT and neutropenia < 1 x 10^9 cells/L were common.* This was agreed.

Given the clinical picture of severe Covid-19 and the short intended treatment duration for baricitinib in these patients, it is accepted that data on hypercholesterolaemia and hypertriglyceridemia had not been collected in ACTT-2, and data were not available from KHAA (**not pursued**).

There is limited safety experience of patients with low values of ALC, ANC and Hb at baseline and during follow-up in the studies. From the limited information there are no indications for safety issues in the Covid-19 trials. The statement 'There is limited information on the use of Olumiant in patients with ALC< 0.2 x 109 cells/L, ANC< 1 x 109 cells/L , or haemoglobin < 8 g/dL.' is therefore acceptable.

Vital signs

In the pooled data, there were no differences between baricitinib and placebo groups in proportions with treatment emergent low/high vital signs (systolic blood pressure, heart rate, respiratory rate, temperature).

CHMP's assessment

The reported vital signs do not give rise to safety concerns.

Safety in special populations and situations

Concomitant use of corticosteroids

The safety results are presented for the two trials separately.

In both treatment groups of study **ACTT-2**, the frequencies of AEs and SAEs were higher in the subgroup of patients who received corticosteroids at baseline.

Treatment-emergent adverse events were reported in 60% of the patients in the baricitinib + remdesivir + steroid group compared with 58.8% of the patients in the placebo + remdesivir + steroid group, while the frequency of SAEs was lower in the group that used baricitinib + remdesivir + steroid compared to placebo + remdesivir +steroid (28.0% versus 31.4%, respectively).

Treatment-emergent adverse events for the infections and infestations SOC were less frequently reported in the baricitinib + remdesivir + steroid group (16%) versus placebo + remdesivir + steroids (19.6%). Serious adverse event frequencies were similar between groups (4% and 3.9%, respectively). Non-Covid-19 infections occurring in the baricitinib group were: urinary tract infection (n=3); oesophageal candidiasis (n=1). Non-Covid-19 infections occurring in the placebo group were: urinary

tract infection (n=1); bacteraemia (n=2), pneumonia staphylococcal (n=1), bronchopulmonary aspergillosis (n=1).

In both treatment groups, the frequencies of AEs and SAEs were higher in the subgroup of patients who received corticosteroids after enrolment.

In study **KHAA**, treatment-emergent adverse events were reported by 42.8% of patients in the baricitinib + SOC group versus 45.6% of patients in the placebo + SOC group, when baseline steroid was prescribed, and 51.7% of patients in the baricitinib + SOC group versus 40.1% of patients in the placebo + SOC group when steroid was *not* prescribed at baseline.

Deaths due to an AE were reported less frequently in the baricitinib + SOC group compared with the placebo + SOC group regardless of baseline steroid use: 1.8% vs. 4.6% with steroids and 0.7% vs. 2.5% without steroids, respectively.

Adverse events leading to permanent study drug discontinuation (including deaths) were less frequently reported in the baricitinib + SOC group compared with the placebo + SOC group (8.6% vs. 10.2%, respectively). For those not on steroids at baseline, AEs leading to permanent study drug discontinuation (including deaths) were reported by 2.8% and 6.2% of patients, respectively.

Infections (excluding Covid-19, pneumonia (sic), septic shock, Covid-19) occurred in 6.1% of patients in the baricitinib + SOC group versus 5.6% of patients in the placebo + SOC group, when baseline steroid was prescribed.

Treatment-emergent adverse events reported by at least 2% of patients in the baricitinib + SOC group taking steroids at baseline compared with patients in the placebo + SOC group taking steroids at baseline were as follows:

- Constipation (4.6% vs. 3.1%)
- Hyperglycaemia (4.0% vs. 3.1%)
- Hypotension (3.8% vs. 2.2%)
- Acute kidney injury (3.8% vs. 3.1%)
- COVID-19 pneumonia (3.6% vs. 3.7%)
- Pneumonia (3.1% vs. 2.9%)
- Acute respiratory failure (2.8% vs. 3.9%)
- Transaminases increased (2.8% vs. 2.2%)
- Pulmonary embolism (2.3% vs. 1.5%)
- Septic shock (2.1% vs. 3.6%)
- Anaemia (2.0% vs. 1.2%)
- Thrombocytosis (2.0% vs. 0.5%)

The frequency of reported SAEs in patients with baseline steroid use was 15.7% in the baricitinib + SOC group compared with 19% in the placebo + SOC group. For those without baseline steroid use, the SAE frequencies were 10.3% and 14.2% for the baricitinib + SOC and placebo + SOC groups respectively.

Serious adverse events reported by at least 2% of patients in the baricitinib + steroid at baseline group compared with the placebo + steroid at baseline group were:

- COVID-19 pneumonia (3.5% vs. 3.2%)

- Acute respiratory failure (2.8 % vs. 4.4%)
- Septic shock (2.0% vs. 3.4%), and
- Pulmonary embolism (2.0% vs. 1.2%).

CHMP's assessment

The use of concomitant steroids was different in both trials and used in different numbers. Therefore, both trials are discussed separately. From both trials, ACTT-2 and KHAA, it does not appear that concomitant use of corticosteroids leads to a different safety profile of baricitinib versus placebo compared to the overall results. Safety assessment of the use of baricitinib with concomitant corticosteroids mostly relies on the results of trial KHAA, that generally has positive safety results. Most notably, attributable non-Covid-19 serious infections were somewhat more frequent on baricitinib as compared to placebo.

Nevertheless, the MAH has provided the table of the overview of adverse events by corticosteroid use at baseline, corticosteroid use after enrolment, dexamethasone use at baseline, and dexamethasone use after enrolment for the integrated analysis (pooled ACCT-2 and KHAA studies), and has discussed it. In all these 4 subpopulations, the proportion of patients with TEAEs was similar or slightly lower in the baricitinib group (43.4%, 57%, 43.2% and 51.9%, respectively) compared to the placebo group (45%, 60.6%, 44.9% and 56.6%). However, the proportion of patients with TEAE related to treatment was slightly increased in each subpopulation in baricitinib group (9.9%, 9%, 10%, and 11.7%) compared to placebo group (6.6%, 8.1%, 6.9% and 8.3%). Compared to patients in the placebo group, and irrespective of corticosteroid/ dexamethasone subgroup, patients in the baricitinib group presented with lower proportions of deaths, deaths due to study disease, deaths due to AEs, SAEs, and permanent discontinuation from study treatment due to an AE. Therefore, overall, the overview of adverse events by corticosteroid use at baseline, corticosteroid use after enrolment, dexamethasone use at baseline, and dexamethasone use after enrolment did not suggest additional safety concerns for the integrated analysis.

Overall, from the safety perspective, baricitinib can be used with concomitant corticosteroids.

Renal impairment

Baricitinib exposure increases with decreased renal function. Based on PK analysis, and in line with recommendations for currently approved indications, dose adjustment is not required for patients with eGFR ≥60 mL/minute/1.73 m^2. The suggested dose for patients with moderate renal impairment (eGFR between 30 and 60 mL/minute/1.73 m^2) is 2 mg of baricitinib daily.

For the treatment of patients with Covid-19 and impaired renal function, the MAH proposes for section 4.2 that, the recommended dose of Olumiant in patients with estimated glomerular filtration rate (GFR) between 15 and 30 mL/ minute/1.73 m^2 is 2 mg once every 48 hours. Baricitinib is not recommended for use in patients with estimated GFR of < 15 mL/min.

Patients with an estimated glomerular filtration rate <30 mL/ minute/1.73 m^2 have not been included in studies ACTT-2 or KHAA. No data are available.

CHMP's assessment

For patients with moderate renal impairment (eGFR between 30 and 60 mL/minute/1.73 m2) the proposed dose is 2 mg of baricitinib daily. This is similar for patients with Covid-19 and patients with

Rheumatoid arthritis or Atopic dermatitis. For patients with Covid-19 and an estimated glomerular filtration rate (GFR) between 15 and 30 mL/min/1.73 m^2, the proposed dose is 2 mg once every 48 hours (one in 2 days). For patients with lower glomerular filtration rates, baricitinib is not recommended.

It is referred to the Pharmacokinetics section for a discussion regarding the justification for the dose in patients with Covid-19 and an estimated glomerular filtration rate (GFR) between 15 and 30 mL/min.

Hepatic impairment

Population PK analysis of patients with RA suggests that no dose adjustment is necessary in patients with mild or moderate hepatic impairment. As stated in the SmPC, baricitinib has not been studied in patients with severe hepatic impairment. It is not known if dosage adjustment is needed in patients with severe hepatic impairment.

CHMP's assessment

For baricitinib, no dose adjustment is required in patients with mild or moderate hepatic impairment. In Rheumatoid arthritis and Atopic dermatitis, baricitinib is not recommended for use in patients with severe hepatic impairment. For the indication with Covid-19 the MAH proposes to add to the SmPC: 'Olumiant has not been studied in patients with severe hepatic impairment'.

The statement is considered acceptable, given the short treatment duration of up to 14 days and the seriousness of the underlying condition. Patients with Covid-19 are well monitored when being in intensive care. It appears to be appropriate that it is left to the prescriber to make an individual weighing of Benefit/Risk for patients with Covid-19 and severe hepatic impairment.

No clinical studies with baricitinib were performed in patients with severe hepatic impairment. Patients with severe hepatic impairment often have serious co-morbidities, which calls for caution when considering pharmacological treatment. Therefore, the use of baricitinib in patients with severe hepatic impairment is not recommended for the treatment of RA or AD.

Pregnancy

Effects of baricitinib on human foetal development are not known. The JAK-STAT pathway has been shown to be involved in cell adhesion and cell polarity, which can affect early embryonic development.

Olumiant is contraindicated during pregnancy (see SmPC sections 4.3 and 4.6). Women of childbearing potential have to use effective contraception during and for at least 1 week after treatment. If a patient becomes pregnant while taking Olumiant the parents should be informed of the potential risk to the foetus. For the treatment of Covid-19, the MAH considers that, due to the unmet medical need in treatment of severe COVID-19 and the short duration of treatment, the potential benefits of the use of baricitinib in pregnant females should be weighed against the potential risk to the foetus. For the SmPC it is proposed:

'COVID 19

…

Olumiant should not be used during pregnancy unless the clinical condition of the woman requires treatment with baricitinib.'

Pregnancy was an exclusion criterion for studies ACTT-2 and KHAA. In ACTT-2, no women became pregnant during study participation and no pregnancies were reported in the CSR of KHAA.

CHMP's assessment

Baricitinib is contra-indicated during pregnancy. In rat and rabbit reproductive toxicology studies, baricitinib was shown to reduce foetal growth/weight and produce skeletal malformations (at exposures of approximately 10 and 39 times the human exposure, respectively). No adverse foetal effects were observed at exposures 2 times the human exposure based on AUC. [SmPC section 5.3]

For the treatment of Covid-19 however, the MAH proposes a warning instead of a contra-indication. Given the short treatment duration and the life-threatening nature of Covid-19, weighing Benefit/Risk for Covid-19 differs from the treatment of Rheumatoid arthritis and Atopic dermatitis. Also, there currently are no alternative treatment options other than corticosteroids, though the use of corticosteroids in pregnancy also poses a risk for the unborn [e.g. Neofordex SmPC]. This means that for the treatment of Covid-19 in case of pregnancy, a strict warning instead of a contra-indication can be accepted.

Elderly

The MAH considers that age did not influence the number of TEAEs or SAEs across the age groups analysed; and since patients are being monitored in a hospital environment and will be treated for a short period of time, the recommendation for a dose reduction in special populations (patients such as those aged 75 years or older, for patients with a history of chronic or recurrent infections) is not considered appropriate in the COVID-19 patient population.

The number of deaths across age groups, in both ACTT-2 and KHAA, was consistently lower for the baricitinib treated group compared to placebo, except for the group of patients over 85 years in Study KHAA (Table 58). Data from both studies combined show no differences in the frequency of death reported for those >85 years of age for baricitinib treated patients (28.1%, n=9) and placebo (28%, n=7). In Study KHAA, 8 deaths were reported in the baricitinib treated group versus 3 in the placebo treated group, which is in contrast to what was reported by the ACTT-2 Study (1 death in the baricitinib treated group versus 4 in the placebo treated group).

Infection-related TEAEs and SAEs were reported for a similar percentage of patients in the baricitinib treated group in both Study ACTT-2 and Study KHAA across age groups. Pooled data from both studies show no meaningful differences in the frequency of infections between the baricitinib treated group and the placebo treated group.

Table 58 ***Overview of Selected Adverse Events by Age Category, Safety Population, BARI COVID-19 PC Analysis Set (Studies ACTT-2 and KHAA)***

	<65 Years		65 to 74 Years		75 to 84 Years		>=85 Years	
Event Category	PBO (N=865) n (%)	BARI 4-mg (N=862) n (%)	PBO (N=253) n (%)	BARI 4-mg (N=243) n (%)	PBO (N=118) n (%)	BARI 4-mg (N=120) n (%)	PBO (N=25) n (%)	BARI 4-mg (N=32) n (%)
Total TEAEs	352 (40.7)	334 (38.7)	138 (54.5)	115 (47.3)	72 (61.0)	73 (60.8)	14 (56.0)	22 (68.8)
SAEs	126 (14.6)	104 (12.1)	60 (23.7)	48 (19.8)	49 (41.5)	34 (28.3)	9 (36.0)	11 (34.4)
Fatal	25 (2.9)	15 (1.7)	17 (6.7)	11 (4.5)	22 (18.6)	8 (6.7)	4 (16.0)	1 (3.1)
Hospitalisation	61 (7.1)	62 (7.2)	29 (11.5)	19 (7.8)	19 (16.1)	13 (10.8)	2 (8.0)	3 (9.4)
Life-threatening	73 (8.4)	61 (7.1)	36 (14.2)	28 (11.5)	24 (20.3)	15 (12.5)	4 (16.0)	7 (21.9)
Disability	5 (0.6)	4 (0.5)	2 (0.8)	1 (0.4)	5 (4.2)	0	0	0
Other	5 (0.6)	11 (1.3)	3 (1.2)	4 (1.6)	1 (0.8)	6 (5.0)	2 (8.0)	1 (3.1)
AE leading to permanent discontinuation of the study drug	54 (6.2)	40 (4.6)	31 (12.3)	20 (8.2)	20 (16.9)	15 (12.5)	5 (20.0)	7 (21.9)
Psychiatric disorders (SOC)	17 (2.0)	28 (3.2)	16 (6.3)	7 (2.9)	5 (4.2)	7 (5.8)	1 (4.0)	3 (9.4)
Nervous system disorders (SOC)	22 (2.5)	23 (2.7)	8 (3.2)	5 (2.1)	2 (1.7)	5 (4.2)	0	2 (6.3)
Accidents and injuries (SMQ)	7 (0.8)	4 (0.5)	4 (1.6)	1 (0.4)	3 (2.5)	6 (5.0)	0	0
Cardiac disorders (SOC)	23 (2.7)	26 (3.0)	19 (7.5)	11 (4.5)	10 (8.5)	10 (8.3)	2 (8.0)	4 (12.5)

Vascular disorders (SOC)	56 (6.5)	47 (5.5)	32 (12.6)	20 (8.2)	6 (5.1)	20 (16.7)	4 (16.0)	5 (15.6)
Infections and infestations (SOC)	102 (11.8)	75 (8.7)	41 (16.2)	46 (18.9)	35 (29.7)	29 (24.2)	5 (20.0)	9 (28.1)
Cerebrovascular disorders	5 (0.6)	3 (0.3)	3 (1.2)	1 (0.4)	0	3 (2.5)	0	0
Anticholinergic syndrome	0	0	0	0	0	0	0	0
Quality of life decreased	0	0	0	0	0	0	0	0
Postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures and related AEs	3 (0.3)	0	2 (0.8)	0	0	3 (2.5)	0	0
AE appearing more frequently in >65 years	176 (20.3)	162 (18.8)	85 (33.6)	72 (29.6)	55 (46.6)	40 (33.3)	8 (32.0)	15 (46.9)

Abbreviations: AE = adverse event; n = patients with >=1 event; SAE = serious adverse event; SMQ = standardized MedDRA query; SOC = system organ class; TEAE = treatment-emergent adverse event.
PBO and BARI 4-mg groups includes RDV from ACTT-2.
MedDRA Version 23.0 for ACTT-2 and MedDRA Version 23.1 for KHAA.

CHMP's assessment

From the currently provided data, it does not appear that baricitinib overall leads to more AEs than placebo, over all age groups. Above 85 years, the occurrence of AEs increases, and there appears to be a tendency for a higher risk of AEs when treated with baricitinib, as compared to placebo. In study KHAA, a numerical mortality advantage was present over all age classes except for patients ≥85 years, where there was a numerical disadvantage of baricitinib where about half of the patients died (8/15) versus placebo (3/9) where this was one-third. Due to the low numbers, this might be a chance finding and a detrimental effect of baricitinib on survival was not visible in ACTT-2. The ACTT-4 data confirm a survival benefit of patients >85 years, when treated with baricitinib (3/21 = 14% died) as compared to dexamethasone (30% died), on a background of remdesivir, although patient numbers are small. This issue was considered closed following responses to 2nd RSI; however, in the now submitted data of the RECOVERY trial (see efficacy MO) no treatment effect was shown for patients ≥80 years of age as similar proportions of patients on baricitinib died (130/341 = 38%), as compared to patients on 'usual care' (102/267 = 38%); the effect in patients aged 70 – 80 already was smaller than the effect in patients <70 years of age, pointing to an age-effect-relationship. Consequently, in elderly patients there is no indication that baricitinib is more deleterious than usual care. However, given the RECOVERY data, presence of a treatment effect of baricitinib on mortality in patients >80 years of age is especially questionable (see efficacy section).

Paediatric population

CHMP's assessment

The MAH withdrew the paediatric indication (see PK assessment).

Safety related to drug-drug interactions and other interactions

No new drug interactions have been identified in ACTT-2. Relevant to the safety of the use of baricitinib in COVID-19 is the half-life of approximately 12 hours, which leads to a short washout period once discontinued. Also, a low CYP inhibitory activity determines a low risk of drug to drug interactions. These features allow baricitinib use concomitantly with background therapies.

Remdesivir and dexamethasone are not known to inhibit OAT3 inhibitor, thus they are not expected to impact the PK of baricitinib. The metabolites of remdesivir, GS-704277 and GS-441524, are substrates ofOATP1B1 and OATP1B3. Based on its DDI profile, baricitinib is unlikely to affect the PK of remdesivir or its metabolites. Dexamethasone is a substrate for both CYP3A and Pgp. Since baricitinib does not inhibit CYP3A, nor Pgp, it is unlikely that baricitinib would affect the PK of dexamethasone.

As baricitinib has not been studied in combination with biologic immunomodulators, combination with these drugs is not recommended, as a risk of additive immunosuppression cannot be excluded.

CHMP's assessment

Drug-drug interactions of baricitinib with remdesivir or with corticosteroids are not expected.

Discontinuation due to adverse events

In the **pooled data**, the proportion of AEs leading to permanent discontinuation from the study drug, excluding death due to AE, was lower (p=0.038) in the baricitinib group (6.5%) as compared with the placebo group (8.7%). In both the single studies ACTT-2 and KHAA, the proportion of AEs leading to discontinuation was lower in the baricitinib group compared with the placebo group (not shown).

The AEs that led to discontinuations in the baricitinib group and the placebo group most commonly were: Infections (Covid-19 related and other infections), Investigations (hepatic and renal function), Respiratory disorders (pulmonary embolism and respiratory distress/failure), Renal disorders (acute kidney injury and renal failure/impairment), Vascular disorders (deep vein thrombosis and other thrombotic events), see Table 59. Some numerical differences between baricitinib and placebo appeared in: non-Covid-19 infections (9 *versus* 5); pulmonary embolism (6 *versus* 1) but not deep vein thrombosis (7 *versus* 10); acute kidney injury (20 *versus* 11).

Table 59 AEs leading to permanent discontinuation of study drug, in the combined studies ACTT-2 and KHAA.

System Organ Class Preferred Term	PBO (N=1261) n (%)	IR [PYR]	BARI 4-mg (N=1257) n (%)	IR [PYR]	BARI 4-mg vs. PBO OR 95% CI(a)	p-value (b)
Patients with >= 1 AE	110 (8.7)	394.09 [27.91]	82 (6.5)	297.45 [27.57]	0.7 (0.5, 1.0)	0.038
Infections and infestations	29 (2.3)	103.12 [28.12]	33 (2.6)	119.34 [27.65]	1.1 (0.7, 1.9)	0.599
COVID-19 pneumonia	14 (1.1)	49.79 [28.12]	14 (1.1)	50.59 [27.67]	1.0 (0.5, 2.1)	0.995
COVID-19	1 (0.1)	3.56 [28.07]	5 (0.4)	18.10 [27.63]	5.0 (0.6, 43.2)	0.102
Pneumonia	2 (0.2)	7.13 [28.06]	2 (0.2)	7.24 [27.63]	1.0	0.998
Sepsis	0	0.00 [28.07]	2 (0.2)	7.25 [27.60]	NA	0.157
Septic shock	7 (0.6)	24.93 [28.07]	2 (0.2)	7.24 [27.63]	0.3c	0.097
Aspergillus infection	1 (0.1)	3.56 [28.07]	1 (0.1)	3.62 [27.62]	1.0	0.998
Bacteraemia	0	0.00 [28.07]	1 (0.1)	3.62 [27.63]	NA	0.317
Clostridium difficile infection	0	0.00 [28.07]	1 (0.1)	3.62 [27.61]	NA	0.317
Escherichia bacteraemia	0	0.00 [28.07]	1 (0.1)	3.62 [27.63]	NA	0.317
Lower respiratory tract infection	0	0.00 [28.07]	1 (0.1)	3.62 [27.64]	NA	0.317
Pneumonia bacterial	1 (0.1)	3.56 [28.07]	1 (0.1)	3.62 [27.62]	1.0	0.999
Pulmonary tuberculosis	0	0.00 [28.07]	1 (0.1)	3.62 [27.63]	NA	0.317
Staphylococcal bacteraemia	0	0.00 [28.07]	1 (0.1)	3.62 [27.63]	NA	0.317
Stenotrophomonas infection	0	0.00 [28.07]	1 (0.1)	3.62 [27.63]	NA	0.317
Klebsiella infection	1 (0.1)	3.56 [28.07]	0	0.00 [27.63]	0.0	0.319
Listeriosis	1 (0.1)	3.56 [28.07]	0	0.00 [27.63]	0.0	0.318
Urosepsis	1 (0.1)	3.56 [28.07]	0	0.00 [27.63]	0.0	0.319
Investigations	15 (1.2)	53.49 [28.04]	12 (1.0)	43.40 [27.65]	0.8 (0.4, 1.7)	0.568
Transaminases increased	5 (0.4)	17.82 [28.07]	6 (0.5)	21.71 [27.64]	1.2 (0.4, 4.0)	0.759
Alanine aminotransferase increased	2 (0.2)	7.13 [28.06]	3 (0.2)	10.86 [27.64]	1.5	0.652
Aspartate aminotransferase increased	2 (0.2)	7.13 [28.06]	3 (0.2)	10.86 [27.63]	1.5	0.651
Glomerular filtration rate decreased	4 (0.3)	14.25 [28.07]	1 (0.1)	3.62 [27.63]	0.2	0.181
Creatinine renal clearance decreased	1 (0.1)	3.56 [28.06]	0	0.00 [27.63]	0.0	0.319
Hepatic ensyme increased	1 (0.1)	3.56 [28.07]	0	0.00 [27.63]	0.0	0.318
Respiratory, thoracic and mediastinal disorders	15 (1.2)	53.63 [27.97]	12 (1.0)	43.43 [27.63]	0.8 (0.4, 1.7)	0.568
Pulmonary embolism	1 (0.1)	3.56 [28.07]	6 (0.5)	21.72 [27.62]	6.0 (0.7, 50.3)	0.058
Respiratory failure	5 (0.4)	17.82 [28.07]	3 (0.2)	10.86 [27.63]	0.6	0.482
Acute respiratory failure	8 (0.6)	28.60 [27.97]	2 (0.2)	7.24 [27.64]	0.2	0.058
Respiratory arrest	0	0.00 [28.07]	1 (0.1)	3.62 [27.63]	NA	0.317
Acute respiratory distress syndrome	1 (0.1)	3.56 [28.07]	0	0.00 [27.63]	0.0	0.319

Renal and urinary disorders	24 (1.9)	85.61 [28.03]	11 (0.9)	39.81 [27.63]	0.5 (0.2, 0.9)c	0.028
Acute kidney injury	20 (1.6)	71.34 [28.03]	11 (0.9)	39.81 [27.63]	0.5 (0.3, 1.1)c	0.105
Renal failure	3 (0.2)	10.69 [28.07]	0	0.00 [27.63]	0.0	0.084
Renal impairment	1 (0.1)	3.56 [28.07]	0	0.00 [27.63]	0.0	0.318
Vascular disorders	14 (1.1)	49.96 [28.02]	8 (0.6)	29.04 [27.55]	0.6 (0.2, 1.4)	0.201
Deep vein thrombosis	10 (0.8)	35.68 [28.03]	7 (0.6)	25.39 [27.57]	0.7 (0.3, 1.8)	0.470
Embolism venous	1 (0.1)	3.56 [28.08]	1 (0.1)	3.62 [27.61]	1.0	0.998
Axillary vein thrombosis	1 (0.1)	3.56 [28.07]	0	0.00 [27.63]	0.0	0.319
Peripheral ischaemia	1 (0.1)	3.56 [28.05]	0	0.00 [27.63]	0.0	0.319
Thrombosis	1 (0.1)	3.56 [28.06]	0	0.00 [27.63]	0.0	0.319
Gastrointestinal disorders	2 (0.2)	7.12 [28.07]	2 (0.2)	7.24 [27.62]	1.0	0.998
Diarrhoea	0	0.00 [28.07]	1 (0.1)	3.62 [27.63]	NA	0.317
Dysphagia	0	0.00 [28.07]	1 (0.1)	3.62 [27.62]	NA	0.317
Ileus paralytic	1 (0.1)	3.56 [28.08]	0	0.00 [27.63]	0.0	0.318
Vomiting	1 (0.1)	3.56 [28.06]	0	0.00 [27.63]	0.0	0.319
General disorders and administration site conditions	5 (0.4)	17.81 [28.07]	2 (0.2)	7.24 [27.64]	0.4	0.259
Multiple organ dysfunction syndrome	3 (0.2)	10.69 [28.07]	2 (0.2)	7.24 [27.64]	0.7	0.658
Injection site induration	1 (0.1)	3.56 [28.07]	0	0.00 [27.63]	0.0	0.319
Pyrexia	1 (0.1)	3.56 [28.07]	0	0.00 [27.63]	0.0	0.319
Cardiac disorders	5 (0.4)	17.81 [28.08]	1 (0.1)	3.62 [27.63]	0.2	0.103
Cardio-respiratory arrest	3 (0.2)	10.69 [28.07]	1 (0.1)	3.62 [27.63]	0.3	0.319
Cardiac arrest	1 (0.1)	3.56 [28.07]	0	0.00 [27.63]	0.0	0.319
Left ventricular failure	1 (0.1)	3.56 [28.07]	0	0.00 [27.63]	0.0	0.319
Hepatobiliary disorders	2 (0.2)	7.12 [28.07]	1 (0.1)	3.62 [27.63]	0.5c	0.566
Hepatic function abnormal	0	0.00 [28.07]	1 (0.1)	3.62 [27.63]	NA	0.317
Hepatitis	1 (0.1)	3.56 [28.07]	0	0.00 [27.63]	0.0	0.319
Liver injury	1 (0.1)	3.56 [28.07]	0	0.00 [27.63]	0.0	0.319
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0.00 [28.07]	1 (0.1)	3.62 [27.61]	NA	0.317
Lipoma	0	0.00 [28.07]	1 (0.1)	3.62 [27.61]	NA	0.317
Nervous system disorders	0	0.00 [28.07]	1 (0.1)	3.62 [27.61]	NA	0.317
Cerebrovascular accident	0	0.00 [28.07]	1 (0.1)	3.62 [27.61]	NA	0.317
Blood and lymphatic system disorders	5 (0.4)	17.83 [28.04]	0	0.00 [27.63]	0.0	0.026
Lymphopenia	4 (0.3)	14.26 [28.04]	0	0.00 [27.63]	0.0	0.046
Neutropenia	1 (0.1)	3.56 [28.07]	0	0.00 [27.63]	0.0	0.319
Immune system disorders	1 (0.1)	3.56 [28.07]	0	0.00 [27.63]	0.0	0.319
Hypersensitivity	1 (0.1)	3.56 [28.07]	0	0.00 [27.63]	0.0	0.319
Skin and subcutaneous tissue disorders	1 (0.1)	3.56 [28.07]	0	0.00 [27.63]	0.0	0.319
Rash	1 (0.1)	3.56 [28.07]	0	0.00 [27.63]	0.0	0.319

Abbreviations: IR = incidence rate; N = number of patients in the analysis population; n = number of patients in the specified category; OR = Mantel-Haenszel odds ratio; PYR = patient-years at risk.

CHMP's assessment

Overall, there were no large numerical differences between baricitinib and placebo in the occurrence of AEs that lead to permanent discontinuation of study drug, except for non-Covid-19 infections and pulmonary embolism, which were numerically more frequent in the baricitinib group. Pulmonary embolism as reason for discontinuation also was more frequent in the baricitinib group as compared to placebo (6 versus 1), but deep vein thrombosis was not (7 versus 10). The pattern of occurrence of AEs leading to permanent discontinuation in the pooled data was overall in line with the results of the individual studies (not shown).

Post marketing experience

Baricitinib 2 mg and 4 mg was first authorised on 13 February 2017 in the EU to treat moderate to severe active RA in adult patients; since then, it has been authorised in 75 other countries. For AD, baricitinib was first authorised on 19 October 2020 in the EU to treat moderate to severe AD in adult patients; since then, it has been approved in 34 other countries.

As of 31 May 2021, an estimated 317,000 patients have been exposed to baricitinib globally for the treatment of COVID-19. This estimate was calculated by dividing the total number of milligrams sold by the estimated average daily dose (4mg) to obtain the total days of therapy. The total days of therapy were then divided by the estimated average length of therapy (7.5 days in the US and 10 days in all other countries/regions) for an individual patient to obtain the estimated number of patients exposed.

As of 27 June 2021, 85 post-authorization reports of AEs have been received from patients treated with baricitinib for the coronavirus/COVID-19 indication. Of these 85 reports, 34 were off-label use and 51 were in patients treated for COVID-19 under the US Emergency Use Authorisation.

These 85 reports included 267 events, of which 203 were serious and 64 were nonserious.

A fatal outcome was present in 27 of the 85 reports. In these 85 reports, the events that were most frequently reported or are related to recognised risks of baricitinib included:

- acute kidney injury (n = 7), renal impairment (n = 3) and renal failure (n =1)
- death (n = 10)
- septic shock (n = 8)
- DVT/PE (n = 4), thrombosis (n = 2) and embolism venous (n = 1)
- fungal infections ([n = 4] including candida infection [n = 1], bronchopulmonary aspergillosis [n = 1]) and fungal infection [n = 2],
- stroke (n = 2)
- sepsis (n = 1)
- small intestinal perforation (n = 1)

Where information was available, the majority of these reports presented confounding risk factors for the reported events or the AEs were known complications of the COVID-19 infection.

CHMP's assessment

There is substantial exposure (more than 300 thousand patients) to baricitinib in the coronavirus/COVID-19 indication. Majority of the reported events was serious (203 out of 267 events). According to the MAH, there were 44 events (with seriousness unspecified) classified as being most frequently reported or being related to recognized risks of baricitinib. Most frequently reported adverse events were: acute kidney injury (n = 7), renal impairment (n = 3) renal failure (n =1); death (n = 10); septic shock (n = 8); and DVT/PE (n = 4), thrombosis (n = 2) and embolism venous (n = 1). Information was lacking about the other 223 other events. Narratives have not been provided or discussed so it cannot be assessed whether use of baricitinib in the individual cases contributed to the occurrence of any of the reported adverse events. In our view, the details of the post-marketing cases are too sparse to draw reasonable conclusions on new safety signals or risks.

Safety data from supportive study

According to the on-line publication of the RECOVERY trial comparing baricitinib with usual care (https://www.medrxiv.org/content/10.1101/2022.03.02.22271623v1), there were no significant differences in the pre-specified subsidiary clinical outcomes of cause-specific mortality other than

that due to COVID-19 or in use of ventilation, successful cessation of invasive mechanical ventilation, or receipt of haemodialysis or haemofiltration. There were no significant differences in the rates of non-coronavirus infection, thrombotic events, or clinically significant bleeding, but allocation to baricitinib was associated with a nominally significant reduction in new onset 291 cardiac arrythmia (2.3% vs 3.1%, p=0.017). There were 13 reports of a 292 serious adverse reaction believed to be related to treatment with baricitinib, including 5 participants with a serious non-COVID infection, 3 with a bowel perforation and 2 with a pulmonary embolism. Accordingly, it is considered that the available safety results from RECOVERY do not change insights that were gained from the safety data of KHAA and ACTT-2.

2.6.1. Discussion on clinical safety

Existing safety profile

In patients with Rheumatoid arthritis and Atopic dermatitis, the most reported Adverse drug reactions were increased LDL cholesterol, upper respiratory tract infections, and headache. Among the 'common' Adverse drug reactions are viral reactivation (herpes) and pneumonia, while deep venous thrombosis and pulmonary embolism were 'uncommon'. For more information regarding the existing Adverse Drug Reactions, contra-indications, warnings, and the summary of safety concerns, it is referred to the introduction of this safety section and the SmPC.

Design and exposure

In study ACTT-2, only severe and life-threatening AEs (grade 3 and 4) were collected, while in study KHAA the AEs that were mild (grade 1), moderate (grade 2), severe, or life-threatening AEs were collected. In the context of short-term treatment of hospitalised patients with Covid-19, it is in principle acceptable that in ACTT-2 only information of grade 3 and 4 AEs is available.
Another major difference between the two trials is that in study ACTT-2, baricitinib is compared to placebo on a background of remdesivir while in study KHAA this comparison is performed against a background of 'standard-of-care' which usually (~80%) was corticosteroids. Besides assessing the pooled data, this draws attention to the safety data of the trials separately, especially for (viral) infections. Also, the design of study KHAA may reflect current treatment preference better.

In both trials, ACTT-2 and KHAA, the period of exposure to study drug (up to 14 days) is about half of the observation time of safety events (28 or 29 days). Although the observation period is at least twice if the period of exposition, using this safety follow-up is considered reasonable. This, given the half-life (12 hours) of baricitinib and given that PD effects for safety events may have different time windows after stopping the drug. The patient numbers in both studies, ACTT-2 and KHAA combined as well as separately, are sufficiently large to also detect uncommon adverse events with sufficient certainty, by roughly relying on the 'rule of three' (Eypasch 1995).

Data of the ACTT-4 study and of the RECOVERY trial were not broadly included in the safety discussion. ACTT-2 and KHAA were regarded as main studies. Safety data of the RECOVERY trial was only available through the on-line publication. ACTT-4 was a supportive study with two active treatment arms, and this contrast limits interpretation of safety data.

Adverse events

In the data of studies ACTT-2 and KHAA combined, the occurrence of AEs (43% versus 46%), SAEs (16% versus 19%), deaths 'due to an AE' (2.8% versus 5.4%), discontinuations due to an AE (6.5% versus 8.7%) was overall lower for baricitinib as compared to placebo. These results are in line with the data of studies ACTT-2 and KHAA separately. In study ACTT-2, the proportion of patients with at

least one AE was 42% in the baricitinib group and 48% in the placebo group. In study KHAA, the proportion of patients with at least one AE was 45% in the baricitinib group and 44% in the placebo group. Remind that in study ACTT-2 only severe and life-threatening events (grade 3 and 4) were collected, while in KHAA also mild and moderate (grade 1 and 2) AEs were collected. On the other hand, the differences between treatment groups are consistent over the two trials.

From the pooled and individual data of studies ACTT-2 and KHAA, there appeared to be no new safety signals for baricitinib.

In the pooled data, AEs most frequently occurred (baricitinib *versus* placebo) in the SOCs of Investigations (17% *versus* 18%); Infections and infestations (13% *versus* 15%); Respiratory, thoracic and mediastinal disorders (13% *versus* 15%); Vascular disorders (7.3% *versus* 7.8%); Blood and lymphatic system disorders (7.1% *versus* 7.1%), without large differences between the two treatment groups. Of the most common (≥2%) AEs in the pooled data, there only were two that occurred numerically more often with baricitinib as compared to placebo: glomerular filtration rate decreased (4.0% versus 3.6%) and constipation (2.6 versus 1.8%). However, these are not considered as (potential) risk of baricitinib:

Glomerular filtration rate decreased was seen more frequently with baricitinib than with placebo, but for acute kidney injury, this was reversed. The differences between baricitinib and placebo in the occurrence of these two renal AEs are small. Other renal AEs in the pooled data (creatinine renal clearance decreased, haematuria, renal failure, renal impairment) also did not point to an imbalance that would be unfavourable of baricitinib. Renal failure or decreased renal function is not a known or potential risk of treatment with baricitinib. Also, renal failure or decreased renal function is not a known or potential risk of treatment with baricitinib. Acute kidney injury with suddenly reduced glomerular filtration rate however is a known complication of Covid-19, which may be caused directly by the virus or indirectly through inflammation and immune dysfunction, and/or through dysfunction of other organs [Nadim et al. 2020 https://www.nature.com/articles/s41581-020-00356-5]. Also, there is a suspicion of renal failure as adverse reaction of remdesivir [Veklury SmPC]. Consequently, based on the available data, (signs of) renal disorder must not be considered as an ADR of baricitinib.

Constipation and diarrhea both occurred in low numbers, but both more frequently with baricitinib as compared to placebo. Constipation and diarrhea are not known as ADRs for baricitinib. Obstipation is quite a common event in severely ill patients at the ICU, which may be due to immobilisation as well as be a consequence of prolonged sedation [Hay et al. 2020 https://doi.org/10.1016/j.jcrc.2019.01.004]. Also, corticosteroids, notably dexamethasone, may cause constipation and diarrhea [Neofordex SmPC]. All cases of constipation and diarrhea were from study KHAA, which could be due to background treatment as constipation and diarrhea are ADRs of corticosteroids, and/or be a consequence of only collecting grade 3 and 4 events in ACTT-2. Given the low occurrence and the known association of obstipation and diarrhea with critically ill patients at the ICU and with corticosteroids, it is not proposed to pursue obstipation and diarrhea as probable ADRs of baricitinib.

In the safety data, several AEs can be found that are synonyms of Covid-19, or likely manifestations, sequelae, or complications of Covid-19. These are reflected by: respiratory failure, acute respiratory failure, pneumonia, septic shock, glomerular filtration rate decreased/acute kidney injury. From the pooled data as well as from the data of the two trials individually (not shown) there is a tendency that AEs reasonably attributable to Covid-19 occur more frequently in the placebo group as compared with the baricitinib group. This means that there currently is no signal that baricitinib would overall worsen Covid-19, or its complications. An exception could be made for VTE, which is a known ADR of baricitinib but also known as a complication of Covid-19.

Serious Adverse Events and deaths

In the pooled data, the proportion of patients with at least one SAE was lower in the baricitinib group (16%), as compared to the placebo group (19%), this was also seen in the individual trials ACTT-2 and KHAA. The most reported SAEs in the baricitinib group as compared to the placebo group were: respiratory failure (3.1% versus 4.3%); acute respiratory failure (2.8% versus 3.6%); septic shock (1.4% versus 3.6%). Also, from the analysis of SAEs, it appears that most SAEs could be attributable to Covid-19. The occurrence of SAEs was higher with baricitinib as compared to placebo for pneumonia bacterial (0.7% versus 0.4%) and pulmonary embolism (1.6% versus 0.9%).

By far most of the deaths in both treatment groups of both trials are reasonably attributable to Covid-19 and its known complications. Study KHAA had a 60 day follow-up. At Day 60 in study KHAA, the difference between baricitinib and placebo was ~5%, which is numerically similar as the difference at Day 29.

The importance of these results is that from both trials there currently is no indication that baricitinib overall leads to more SAEs, or a worsening in Covid-19, as compared to placebo. However, this is less clear for patients >85 years of age.

Adverse Events of Special Interest

From ACTT-2 and KHAA, it did not appear that there was an increased occurrence in patients treated with baricitinib, as compared to placebo, for arterial thrombotic events, major adverse cardiovascular events, and renal events. New infections do not appear to be more frequent with baricitinib. VTE and especially pulmonary embolism were more frequent on baricitinib, as were elevations in AST/ALT.

Infections, including serious and opportunistic infections, are an identified risk for baricitinib. From the pooled data of studies ACTT-2 and KHAA it appears that infections and serious infections occurred less frequently with baricitinib as compared to placebo, and opportunistic infections were not more frequent with baricitinib. By subtracting the presumable Covid-19 AEs from the overall infection AEs, it preliminary seems that the occurrence of new (non-SARS-CoV-2) infections also is lower in the baricitinib group as compared to the placebo group (11% versus 12%). For mentioning in section 4.8 in the SmPC however, the occurrence of new infections and new serious infections should however be cleared by the MAH. The MAH couldn't provide useful information on the course of infections. Apparently the 'non-Covid-19 events' cannot be well disentangled from probable Covid-19 related events and from the course that Covid-19 may take. From the current data, it appears that pneumonia with attributed cause/agent and without attributed cause, occurs less in the baricitinib group as compared to placebo. This is in line with the overall results on infections. The MAH asserted that pneumonia (sic) was not due to Covid-19.

Pulmonary embolism (PE) and **Deep venous thrombosis** (DVT) are ADRs of baricitinib treatment, and VTE is an important potential risk for baricitinib. In the pooled data, treatment-emergent VTEs were reported by 3.3% of patients treated with baricitinib and by 2.8% of patients treated with placebo. This is mainly due to a numerically higher occurrence of PE in patients treated with baricitinib in the pooled data as well as in the individual studies. In both ACTT-2 and KHAA, nearly all patients used prophylactic anti-coagulant treatment. Therefore, it is unlikely that the cases of VTE would be explained by a lack of prophylactic treatment. The SmPC proposals to include a recommendation to use of prophylactic anti-coagulant treatment in Section 4.2 of the SmPC, and to change the frequencies of PE and DVT in section 4.8 to 'common' for Covid-19 are acceptable. Thrombocytosis was confirmed to be ADR in the trials ACTT-2 and KHAA. In the pooled trial data, high platelet levels occurred more in baricitinib treated patients as compared to placebo treated patients (46% *versus* 35%), and thrombocytosis also was more frequent in the baricitinib group (8.2% *versus* 4.3%).

Given the known risk factors for VTE already mentioned in the warning (older age, obesity, a medical history of DVT/PE, or patients undergoing surgery and immobilisation), there seems to be no clear route for further risk minimisation. All patients with Covid-19 have an increased risk for VTE, also without baricitinib [Malas 2021 https://doi.org/10.1016/j.eclinm.2020.100639].

Hepatic events

Increases in hepatic laboratory values for ALT and AST occurred more frequently in the baricitinib group as compared to the placebo group. Hepatic adverse events or serious adverse events did, however, not occur more frequently in the baricitinib group. This is in line with increases in ALT and AST as known ADRs. The occurrence of high ALT and high AST in the Covid-19 trials was much higher, in both treatment groups, as compared to the trials in Rheumatoid arthritis and in Atopic dermatitis. Although the precise influence of Covid-19 on the liver remains unclear, abnormalities in liver biochemistries are common in patients with Covid-19, occurring in approximately 15–65% of SARS-CoV-2-infected individuals [Marjot 2021, https://doi.org/10.1038/s41575-021-00426-4]. It is therefore agreed that the elevations in liver enzymes in the Covid-19 population are separately described in section 4.8 of the SmPC, and that in the ADR table reference is made to the differing occurrence of increases in ALT and AST in Covid-19.

Concomitant use of corticosteroids

Analyses of corticosteroid use at baseline and after enrolment did not suggest additional safety concerns for both studies, and baricitinib could be used with concomitant corticosteroids from a safety perspective. The MAH included in Section 4.2 of the SmPC a statement that "Baricitinib may be used with or without corticosteroids and with or without remdesivir" which is acceptable.

Elderly

From the currently provided data it does not appear that baricitinib overall leads to more AEs than placebo over all age groups.

Renal and hepatic impairment

For patients with Covid-19 and an estimated glomerular filtration rate (GFR) between 15 and 30 mL/min/1.73 m^2, the proposed dose is 2 mg once every 48 hours (one in 2 days). For patients with lower glomerular filtration rates, baricitinib is not recommended. It is referred to the Pharmacokinetic section for a discussion regarding the justification for the dose in patients with Covid-19 and an estimated glomerular filtration rate (GFR) between 15 and 30 mL/min.

Benefit/Risk in the treatment of patients hospitalised because of Covid-19, differs from the Benefit/Risk in Rheumatoid arthritis, Atopic dermatitis and Alopecia Areata. Therefore, it is appropriate to leave the prescriber to make an individual weighing of Benefit/Risk for patients with Covid-19 and severe hepatic impairment, given the severe nature of Covid-19 and the short duration of treatment. A statement has been added in Section 4.2 of the SmPC.

Pregnancy

Pregnancy and breastfeeding were exclusion criteria for ACTT-2 and KHAA. No women became pregnant during study participation in ACCT-2.

Baricitinib is contra-indicated during pregnancy. For the treatment of Covid-19 however, the MAH proposes a warning instead of a contra-indication. Given the short treatment duration and the life-threatening nature of Covid-19, weighing Benefit/Risk for Covid-19 differs from the treatment of Rheumatoid arthritis, Alopecia Areata and Atopic dermatitis. Also, currently the main treatment option is corticosteroids, though the use of corticosteroids in pregnancy also poses a risk for the

unborn [e.g. Neofordex SmPC]. This means that for the treatment of Covid-19 in case of pregnancy, a strict warning including a rationale, instead of a contra-indication, could be accepted.

Patients with low ALC, low ANC, low Hb.

In RA, AD and AA, treatment should not be initiated in patients with a low absolute lymphocyte count(ALC), a low absolute neutrophil count (ANC), or a low haemoglobin (Hb) value. However, the MAH proposed in the SmPC information relevant for Covid-19 that: *'There is limited information on the use of Olumiant in patients with ALC< 0.2 x 109 cells/L, ANC< 1 x 109 cells/L , or haemoglobin < 8 g/dL.'* without reference to not initiate baricitinib. These patients were excluded from the trials. By the MAH, it is reasoned that the severity of the disease in the target population justifies the uncertainty in patients with Covid-19 and severe hepatic failure, pre-existing or new serious infections, low eGFR. For the SmPC the MAH proposes to include that in patients with these conditions 'baricitinib should only be used if the potential benefit outweighs the potential risk'. The statement is considered acceptable, given the seriousness of the underlying condition and given that all patients are standardly monitored, while treatment is for a relatively short period of time.

Safety data from supportive study

According to the on-line publication of the RECOVERY trial comparing baricitinib with usual care (https://www.medrxiv.org/content/10.1101/2022.03.02.22271623v1), there were no significant differences in the pre-specified subsidiary clinical outcomes of cause-specific mortality other than that due to COVID-19 or in use of ventilation, successful cessation of invasive mechanical ventilation, or receipt of haemodialysis or haemofiltration. There were no significant differences in the rates of non-coronavirus infection, thrombotic events, or clinically significant bleeding, but allocation to baricitinib was associated with a nominally significant reduction in new onset 291 cardiac arrythmia (2.3% vs 3.1%, p=0.017). There were 13 reports of a 292 serious adverse reaction believed to be related to treatment with baricitinib, including 5 participants with a serious non-COVID infection, 3 with a bowel perforation and 2 with a pulmonary embolism. Accordingly, it is considered that the available safety results from RECOVERY do not change insights that were gained from the safety data of KHAA and ACTT-2.

Assessment of paediatric data on clinical safety

Currently, no data are available for COVID-19-affected children who were treated with baricitinib. Safety data are available for paediatric patients treated with baricitinib in 3 clinical trials for other therapeutic indications: Juvenile Idiopathic Arthritis (study **JAHV**); Atopic dermatitis (study **JAIP**); Type 1 interferonopathies (Study **JAGA**). About 53 patients in these studies were in the age range 10-18 years.

Initially, the proposed indication statement, included treatment of paediatric patients aged 10 years and older. As no clinical and pharmacokinetic data were provided for the paediatric population, inclusion of the paediatric population in the indication statement was considered not acceptable by the CHMP and a major objection (MO) was raised. In their response, the MAH submitted a revised product information with an indication limited to the proposed indication has been limited to the adult population.

2.6.2. Conclusions on clinical safety

The safety profile of baricitinib is overall positive for the hospitalised adults with COVID-19. The occurrence of AEs, SAEs, discontinuations due to an AE, infections, was lower for baricitinib as

compared to placebo, in both trials. The safety data are consistent with the known safety profile of baricitinib for the approved indications, including infections and VTE. No new safety signals were identified in the treatment of hospitalised adult patients with Covid-19. However, some ADRs, including AST ≥3 × ULN, ALT ≥3 × ULN, PE, DVT, and neutropenia less than 1000 cells/mm^3, were reported more frequently for the COVID-19 population compared to the RA and AD populations.

2.6.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

3. Risk management plan

The MAH submitted an updated RMP version 11.1 (DLP of 17 November 2020), dated 27 January 2021 with this application. The proposed changes concern relevant (safety) information for the new COVID-19 indication. The PRAC assessed the updated RMP.

The main proposed RMP changes were the following:

- Addition of epidemiology of the indication (Part II, Module SI.3), update of clinical trial exposure (Part II, Module SIII), populations not studied/under-represented in clinical trials (Part II, Module SIV) and safety data (Part II, Module SVII.3) regarding the proposed indication of the treatment of coronavirus disease 2019 (COVID 19) in hospitalised adult and paediatric patients aged 10 years and older who require low-flow oxygen or noninvasive ventilation/high-flow oxygen.

- Update of milestone dates for ongoing additional pharmacovigilance activities (Part III). With COVID 19 indication, expansion of one existing study (B016).

- Addition of routine and additional risk minimisation related to myelosuppression, foetal malformation following exposure in utero, VTE, use in very elderly (≥75 Years) and use in paediatric patients (Part V).

- Updates to Annex 2 (same updates described above for Pharmacovigilance Plan), and Annex 7 (new references) (Part VII).

PRAC assessment:

As part of the procedure EMEA/H/C/004085/IB/0021, the integrated RMP v. 10.1 was adopted. But, in the RMP v. 11.1 proposal, the changes already established under the merged RMP v. 10.1 are not introduced in Part I (Dosage in the EEA).

The MAH is requested to use the currently approved RMP v. 10.1 to prepare the final RMP v. 11.1 (or next version proposal). *The use of older out-of-date versions at this stage of the RMP work creates unnecessary confusion about the content of this document.*

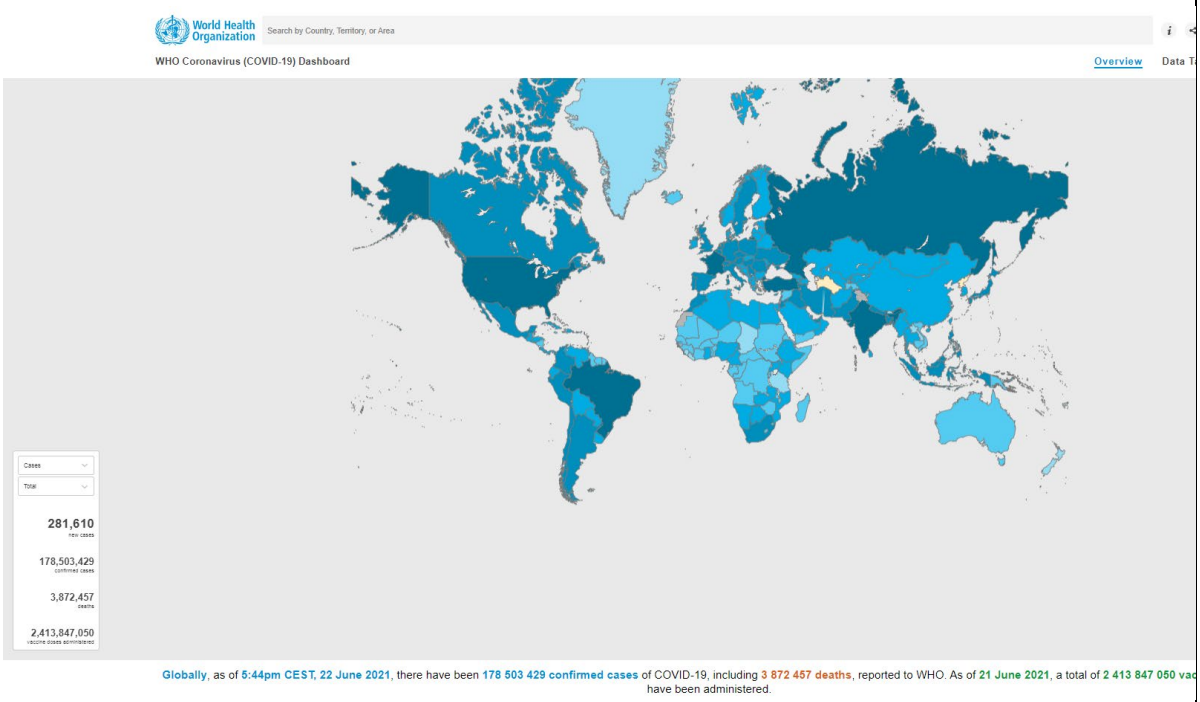
Part II. Safety Specification

Module SI - Epidemiology of the Indications and Target Populations

The MAH included epidemiology of the COVID 19 indication and the target population to be treated. See RMP Module SI for the proposed wordings.

PRAC assessment

The data in Part II section SI.3 are pandemic ones and therefore they change very quickly. Those presented in the RMP v. 11.1 proposal are very out of date - see the data from the website https://covid19.who.int/ Accessed June 22 2021 (the number of confirmed cases is currently approx. 178.5 millions, the number of deaths is currently approx. 3, 87 millions). ***Therefore, this section needs to be updated. It is suggested to add that the epidemic data on COVID-19 change rapidly and the attachment of the appropriate links to check the current data (such as: https://covid19.who.int/*** *or* ***https://www.ecdc.europa.eu/en/cases-2019-ncov-eueea).***



Information on current approved treatment options should be updated*. According to the MAH, the authorized treatment options were last reviewed on December 09, 2020 and meanwhile " the landscape is rapidly changing".*

In addition, the reference Porfidia et al. 2020 – need to be completed in the reference list.

Module SIII. Clinical Trial Exposure

The MAH presented clinical trial exposure of the Adaptive COVID-19 Treatment Trial 2 (ACTT2).

PRAC assessment:

As to be expected given the date of adoption of the RMP v. 11.1 proposal (data lock point for this RMP 17 November 2020 for COVID-19 indication; date of final sign off 27 January 2021), the data

from the KHAA study are not included in this part/module/section or any of the following. ***These data should be completed in all relevant modules/sections of the RMP.***

RMP v. 11.1 proposal contains only data from Adaptive COVID-19 Treatment Trial 2 (ACTT2).

Module SIV. Populations Not Studied in Clinical Trials

SIV.1.1 Exclusion Criteria in a COVID-19 Pivotal Clinical Study within the Development Programme

The MAH newly included this section in the RMP:

Some exclusion criteria utilised in the RA and AD studies were not employed in the single COVID-19 study ACTT2, completed to date. Based on the known safety profile of baricitinib established from the RA and AD population, entry criteria were broadened to more accurately reflect the target population and evaluate baricitinib in situations where it was most likely to be used in clinical practice. **In particular, patients with cardiovascular disease were not excluded from ACTT2.**

In addition, the thresholds for ALT and AST were increased for exclusion from the study; elevation was raised to >5 times the upper limit of normal.

Other exclusion criteria in ACTT2 are consistent with those in the RA and AD studies described in Section SIV.1.

The following important exclusion criteria were specific to the COVID-19 study ACTT2:

Received convalescent plasma or intravenous immunoglobulin [IVIg]) for COVID-19, or 3 or more doses of remdesivir, or small molecule tyrosine kinase inhibitors 1 week prior to screening, or other immunosuppressants in the 4 weeks prior to screening that could impose larger risk compared.

Reason for exclusion: This criterion excluded individuals with recent or concomitant use of specified medications to minimise confounding factors in safety and efficacy data interpretation.

Considered to be included as missing information?: No.

Rationale: Use of convalescent plasma and intravenous immunoglobulin would be expected earlier in the treatment algorithm, in less severely ill patients and hence not relevant to the expected target population.

Use of ≥20 mg/day of prednisone or equivalent for ≥14 consecutive days within the past 4 weeks

Reason for exclusion: This criterion excluded individuals from participating in COVID-19 study ACTT2 who had recent or concomitant use of specified medications to minimise confounding factors in safety and efficacy data interpretation.

Considered to be included as missing information?: No.

Rationale: Study was designed before the effects of dexamethasone were known in COVID-19. Use of high-dose corticosteroids is not standard practice in the management of patients with COVID-19 early in the disease course but is recommended in treatment guidelines for patients requiring supplemental oxygen. Concomitant use of baricitinib with corticosteroids is being evaluated in further studies.

PRAC assessment

The MAH should discuss in RMP Part II Module SIV "Populations not studied in clinical trials" for each excluded patient group, based on both COVID 19 clinical trials, whether this constitutes a safety concern for the intended patient group to be treated for COVID-19 according to the SmPC. In an overall discussion at the end of the Module SIV it can be concluded on whether the current safety concerns under missing information fulfil or need amended.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

The MAH proposed the following changes to this section (**changes bold and underlined**):

Table 60 ***Exposure of Special Populations Included or Not in Clinical Trial Development Programmes***

Type of Special Population	**Exposure**
Pregnant women	Pregnancy was an exclusion criterion in the clinical development programmes; however, 30 pregnancies in maternal exposure (26 in non-AD CTs, including RA, and 4 in AD CTs) and 7 pregnancies from paternal exposure (3 in non-AD CTs and 4 in AD CTs) were reported during the clinical development programmes.
Breastfeeding women	Not included in the clinical development programmes.
Patients with relevant comorbidities:	
Patients with hepatic impairment • Mild to moderate impairment • Severe hepatic impairment	Patients with a history of chronic liver disease and with AST or ALT >1.5 x ULN or total bilirubin ≥1.5 x ULN were not included in the RA clinical development programme. • In a clinical pharmacology study (I4V-MC-JAGC [JAGC], baricitinib was studied in 8 patients with mild to moderate hepatic impairment. • Not studied in patients with severe hepatic impairment. Patients with a history of chronic liver disease or AST or ALT≥2.0 x ULN, alkaline phosphatase ≥2 x ULN, or total bilirubin ≥1.5 x ULN during study screening were not included in the AD programme. Therefore, there was no exposure to patients with ongoing mild to moderate hepatic impairment. ***Patients with ALT or AST >5 times the upper limit of normal were excluded from the COVID-19 study ACTT2.***
Patients with renal impairment • Severe renal impairment • Moderate renal impairment	• Patients with a screening eGFR <30 mL/min/1.73m^2 were excluded. • There were a total of 182 patients in the ALL BARI analysis set (177 RA; 5 AD) with moderate renal impairment at baseline (eGFR <60 mL/min/1.73m^2). • ***Patients with a screening eGFR <30 mL/min or receiving haemodialysis or haemofiltration at the time of screening were excluded from the COVID-19 study ACTT2.***
Patients with cardiovascular impairment	***Patients with myocardial infarction, unstable ischaemic heart disease, stroke, or New York Heart Association Stage IV heart failure within 12 weeks of study entry were excluded from the RA and AD studies but were not explicitly excluded from the COVID-19 study ACTT2.*** Baricitinib has not been specifically studied in patients with cardiovascular impairment.
Immunocompromised patients	Baricitinib has not been specifically studied in immunocompromised patients.

Patients with a disease severity different from inclusion criteria in clinical trials	The RA clinical development programme included a representative population of patients with moderately to severely active RA, including patients who were MTX-naïve, inadequate responders to MTX, and inadequate responders to cDMARDs. In addition, baricitinib was studied in patients with moderately to severely active RA who previously failed one or more TNF inhibitor, representing patients considered to be the least likely to respond to treatment. The AD clinical development programme included a representative population of patients with moderate-to-severe AD, who are candidates for systemic therapy. ***The COVID-19 clinical study ACTT2 included a representative population of patients hospitalised with COVID-19 with Ordinal Scale 4 (not requiring supplemental oxygen), 5 (requiring supplemental oxygen), 6 (high-flow oxygen), or 7 (invasive mechanical ventilation) at baseline.***
Population with relevant different ethnic origin	Per data presented in Module SIII, the distribution of patients of different ethnic origins is generally reflective of the anticipated target population.
Subpopulations carrying relevant genetic polymorphisms	Not applicable.
Other	Not applicable.

Abbreviations: ACTT-2 = Adaptive COVID-19 Treatment Trial 2; AD = atopic dermatitis; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BARI = baricitinib; cDMARD = conventional disease-modifying antirheumatic drug; COVID-19 = coronavirus disease 2019; CT = clinical trial; eGFR = estimated glomerular filtration; MTX = methotrexate; RA = rheumatoid arthritis; TNF = tumour necrosis factor; ULN = upper limit of normal.

PRAC assessment:

As to be expected given the date of adoption of the RMP v. 11.1 proposal (data lock point for this RMP 17 November 2020 for COVID-19 indication; date of final sign off 27 January 2021), the data from the KHAA study are not included in this section or any of the following. ***This data should be completed in all relevant modules/sections of the RMP.***

There are no clinical or pharmacokinetic data available for paediatric population.

Additionally, the MAH is requested to explain why in the ACTT2 study:

- elevated serum activity of liver transaminases to > 5 x upper limit of normal (ULN) was considered an exclusion criterion (not ≥ 2 x ULN, as previously);

- myocardial infarction, unstable ischaemic heart disease, stroke, or New York Heart Association Stage IV heart failure within 12 weeks of study entry, or history or presence of CV disorders that, in the opinion of the investigator could have constituted a risk when taking investigational product were not further considered exclusion criterion;

- the new exclusion criterion was the use of small molecule tyrosine kinase inhibitors (TKIs) 1 week prior to screening.

Module SVII. Identified and Potential Risks

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

The presentation of the important identified risk and important potential risks already included in the RMP of baricitinib have been updated with safety information from Adaptive COVID-19 Treatment Trial 2 (ACTT2).

PRAC assessment

As to be expected given the date of adoption of the RMP v. 11.1 proposal (data lock point for this RMP 17 November 2020 for COVID-19 indication; date of final sign off 27 January 2021), the data from the KHAA study are not included in this part/module/section or any of the following. ***This data should be completed in all relevant modules/sections of the RMP.***

Additionally, the MAH is requested to explain:

- what is the risk of baricitinib use during pregnancy for the fetus, since the benefit of using the drug in this group of patients is to outweigh the risk to the fetus (this is an absolute requirement for the application)?;

- what kind of thromboprophylaxis should be considered during baricitinib administration in COVID-19: what drugs should be used and whether it should be prophylaxis with standard or high-dose of anticoagulant drugs? Where detailed information on thromboprophylaxis during baricitinib administration will be available?

- children were excluded from baricitinib studies in Covid-19 disease (as well as from RA and AD); The total children exposure globally in the CT programme in other disorders = 80 patients, with exposure in the expanded access programme (JAGA) = 71 patients globally; The interim analysis of 14V-MC-B016 study (ongoing procedure No EMEA/H/C/004085/MEA/009.2) identified a total of 6 paediatric patients prescribed off-label baricitinib in the CPRD databases - these comprised 0.63% of all patients (any age) in CPRD prescribed baricitinib; calculated 95% CI spanning 0.23% to 1.37%. Given that the RMP covers only the approved indications and the use of baricitinib in children with COVID-19 is questioned in the CHMP AR for this procedure, "use in pediatric patients" should be removed from the missing information list if the application is withdrawn from the indication "Baricitinib is indicated for the treatment of coronavirus disease 2019 (COVID-19) in hospitalised pediatric patients aged 10 years and higher, who require supplemental oxygen"

Module SVIII - Summary of the Safety Concerns

The MAH proposed the following summary of safety concerns (changes in **bold and underlined**):

Table 61 ***Summary of Safety Concerns*** **[1]**

Summary of Safety Concerns	
Important identified risks	• Herpes zoster
Important potential risks	• Malignancies (including lymphoma and typically virus-induced malignancies such as cervical and many oropharyngeal cancers) • Serious and opportunistic infections (including tuberculosis, *Candida* infections, PML) • Myelosuppression (agranulocytosis) • Myopathy including rhabdomyolysis • Potential for drug-induced liver injury • Gastrointestinal perforation • MACE as an outcome of hyperlipidaemia • Foetal malformation following exposure in utero • VTE
Missing information	• Long-term safety • Use in very elderly (≥75 years) • Use in patients with evidence of hepatitis B or hepatitis C infection • Use in patients with a history of or current lymphoproliferative disease • Use in patients with active or recent primary or recurrent malignant disease • Use in paediatric patients **[2]**

Abbreviations: COVID-19 = coronavirus disease 2019; MACE = major adverse cardiovascular event; PML = progressive multifocal leukoencephalopathy; VTE = venous thromboembolic events.

[1]Per SVII.3, most of the safety concerns identified for baricitinib in the RA and AD indications have not been established for the COVID-19 indication based on lack of reports or potential impact on benefit-risk, particularly in the context of short duration of exposure.

[2]Per SV11.3, this is unlikely to apply to the COVID-19 indication.

PRAC assessment

No new safety concerns have been proposed by the MAH for the treatment of COVID 19 indication.

In the COVID-19 indication VTE occurred more frequently on baricitinib as compared to placebo, especially due to Pulmonary embolism. As Pulmonary embolism and Deep Vein Thrombosis are included as common ADRs in the SmPC section 4.8, the VTE risk may be classified as an important identified risk for the COVID-19 indication instead of an important potential risk as such to be reflected in the list of concerns.

Part III. Pharmacovigilance Plan

III.1. Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific Adverse Event Follow-Up Forms

The following follow-up forms will be used as routine PV materials in order to obtain structured information on reported suspected adverse reactions of special interest for the safety concerns included in the RMP:

- Herpes Zoster
  - HZ follow-up form
- Serious Infections
  - Candida infection follow-up form
  - Pneumonia follow-up form
  - Viral reactivation follow-up form
  - Unspecified infection follow-up form
  - Pulmonary TB follow-up form
  - Extrapulmonary TB follow-up form
- Hepatotoxicity
  - Hepatic disorders follow-up form
- Foetal malformation following exposure in utero
  - Pregnancy data collection - maternal follow-up form
  - Pregnancy data collection - paternal follow-up form
  - Pregnancy outcome - maternal follow-up form
  - Pregnancy outcome - paternal follow-up form
- Venous Thromboembolism
  - Thromboembolic follow-up form
  - Clotting and/or coagulation disorders follow-up form
- Myopathy Including Rhabdomyolysis
  - Rhabdomyolysis follow-up form
- Long-term safety (MACE as an outcome of hyperlipidaemia)
  - Cardiac disorders follow-up form
  - Cerebrovascular accident follow-up form
  - Mortality follow-up form
- Pregnancy
  - Pregnancy data collection - maternal follow-up form
  - Pregnancy data collection - paternal follow-up form
  - Pregnancy outcome - maternal follow-up form
  - Pregnancy outcome - paternal follow-up form

- Breastfeeding follow-up form

- Gastrointestinal perforation
  - Fistula and/or GI perforation follow-up form
- Myelosuppression
  - Blood and bone marrow disorders follow-up form
- Malignancies
  - Cancer/neoplasm follow-up form

PRAC assessment

No changes to the existing follow-up questionnaires for baricitinib have been proposed.

The Follow-up questionnaire for the risk of VTE should be adjusted to provide the possibility to distinguish between an event of Pulmonary embolism and an event of Deep Vein Thrombosis, as now only the general event of VTE can be ticked.

III.2 Additional Pharmacovigilance Activities

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 62 ***Ongoing and Planned Additional Pharmacovigilance Activities***

Study Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 1 - Imposed mandatory additional PV activities that are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional PV activities that are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional PV activities				
I4V-MC-B003: Prospective Observational US Postmarketing safety registry (Corrona) (Ongoing)	Primary Objectives: Compare the incidence rates and profiles of the following aggregate outcomes: serious infections (including herpes zoster) and opportunistic infections (including tuberculosis, *Candida* infections, and PML), MACE, malignancies (including lymphoma and typically virus-induced malignancies, such as cervical and many oropharyngeal cancers), and VTE among patients	Important Identified Risks: Herpes zoster Important potential risks: Serious and opportunistic infections (including tuberculosis, *Candida* infections, PML) MACE as an outcome of hyperlipidaemia Malignancies (including lymphoma and typically	Study progress reports	Annually in PBRER/PSUR submitted in April of each year after start of data collection
			Final study report	31 December 2031

	with long-term exposure to baricitinib versus patients with long-term exposure to other medications used for moderate-to-severe RA; Describe the incidence rates of lymphoma, herpes zoster; opportunistic infections (such as tuberculosis, *Candida* infections, and PML), rhabdomyolysis; myelosuppression (agranulocytosis); hyperlipidaemia (hypercholesterolaemia, hypertriglyceridaemia); GI perforations, and evidence of DILI. Secondary Objective: Describe the incidence of the above outcomes in very elderly patients (aged ≥75 years).	virus-induced malignancies such as cervical and many oropharyngeal cancers) Potential for DILI VTE Myelosuppression (agranulocytosis) Myopathy including rhabdomyolysis GI perforation Missing information: Long-term safety Use in very elderly (≥75 years		
I4V-MC-B004: Retrospective Observational Safety Study Using an Existing Database (Ongoing)	Primary Objectives: To assess and compare the risk of the following aggregate outcomes: serious infections (including herpes zoster) and opportunistic infections (including tuberculosis, *Candida* infections, PML), MACE, malignancies (including lymphoma and typically virus-induced malignancies such as cervical and many oropharyngeal cancers), and VTE, among patients with long-term exposure to baricitinib compared to similar patients with RA with long-term exposure to other indicated medications. To describe the incidence rates of the following	Important Identified Risks Herpes zoster Important potential risks: Serious and opportunistic infections (including tuberculosis, *Candida* infections, PML) MACE as an outcome of hyperlipidaemia Malignancies (including lymphoma and typically virus-induced malignancies such as cervical and many oropharyngeal cancers) Potential for DILI	Study progress reports Final Study Report	Annually in PBRER/PSUR submitted in April of each year after start of data collection 30 June 2030

	individual outcomes: lymphoma; herpes zoster; opportunistic infections such as tuberculosis, *Candida*, and PML; rhabdomyolysis; myelosuppression (agranulocytosis); hyperlipidaemia (hypercholesterolaemia, hypertriglyceridaemia); GI perforations; and evidence of DILI. Secondary Objective: To describe the incidence of the above outcomes in very elderly patients (aged ≥75 years old).	VTE Myelosuppression (agranulocytosis) Myopathy including rhabdomyolysis GI perforation Missing information: Long-term safety Use in very elderly (≥75 years)		
I4V-MC-B011: Retrospective Cohort Study to Assess Safety of Baricitinib in Nordic countries (Ongoing in RA, planned in AD)	Primary Objectives: To compare the incidence rates and profiles of the following aggregate outcomes of serious infections overall (including herpes zoster) and opportunistic infections (including tuberculosis, Candida infections, and PML), MACE, malignancies overall (including lymphoma and typically virus-induced malignancies such as cervical and many oropharyngeal cancers), and VTE, among patients with RA and AD treated with baricitinib versus similar patients treated with other medications indicated for respective condition. To describe the incidence rates of the following individual outcomes: lymphoma; herpes zoster; opportunistic infections such as tuberculosis, *Candida*, and PML; rhabdomyolysis;	Important identified risks: Herpes zoster Important potential risks: Serious and opportunistic infections (including tuberculosis, *Candida* infections, PML) Potential for DILI MACE as an outcome of hyperlipidaemia Malignancy (including lymphoma and typically virus-induced malignancies such as cervical and many oropharyngeal cancers) Foetal malformation following exposure in utero VTE	**For RA study**: Study progress reports Final Report for Objective 4 Final study report	**For RA study:** Annually in PBRER/PSUR submitted in April of each year To be determined based on at least 24 months of data in at least 50% of the discrete healthcare databases 31 December 2027 **For AD Study**:

	agranulocytosis; hyperlipidaemia (hypercholesterolaemia, hypertriglyceridaemia); GI perforations; and liver injury. Secondary Objectives: To monitor the incidence rates of the aggregate outcomes of serious infections overall, MACE, malignancies overall, and VTE in very elderly patients, that is, ≥75 years of age. To assess the effectiveness of risk minimisation activities by describing the pattern of use of baricitinib and the occurrence of pregnancy, active tuberculosis or active viral hepatitis, and the monitoring of lipid levels in relation to baricitinib use in routine clinical care. (This objective complements the aims of Study I4V-MC-B010, which aims to assess the effectiveness of risk minimisation activities.)	Myelosuppression (agranulocytosis) Myopathy including rhabdomyolysis GI perforation Missing information: Long-term safety Use in very elderly (≥75 years)	(Objectives 1-3*)* **For AD Study:** Study progress reports Final Report	Annually in PBRER/ PSUR submitted in April of each year 31 December 2027
I4V-MC-B012 Observational post marketing Surveillance in 3 European Registries (Ongoing)	Primary Objectives: To monitor the incidence rate and profile of the following aggregate outcomes of serious infections (including herpes zoster) and opportunistic infections (including tuberculosis, *Candida* infections, and PML), MACE, malignancies (including lymphoma and typically virus-induced malignancies, such as cervical and many oropharyngeal cancers), and VTE among patients	Important identified Risks: Herpes zoster Important potential risks: Malignancies (including lymphoma and typically virus-induced malignancies such as cervical and many oropharyngeal cancers) Serious and opportunistic infections	Study progress reports Final study report	Annually in PBRER/ PSUR submitted in April of each year 31 March 2024

	with long-term exposure to baricitinib compared to patients with long-term exposure to other medications used for moderate-to-severe RA, as possible given the data available in the BSRBR, RABBIT, and ARTIS registries. To describe the occurrence of the following individual outcomes: lymphoma, herpes zoster, opportunistic infections, rhabdomyolysis, agranulocytosis, PML, GI perforations, and evidence of DILI.	(including Tuberculosis, *Candida* infections, PML), Myelosuppression (agranulocytosis) Myopathy including rhabdomyolysis Potential for drug-induced liver injury GI perforation MACE as an outcome of hyperlipidaemia VTE		
I4V-MC-B016: Assessment of off-label use of baricitinib in the paediatric population in the United Kingdom **(Ongoing)**	Primary objective: Describe the proportion of baricitinib prescribing that occurs off-label to paediatric patients. Secondary objective: If paediatric use is ≥5 patients, describe paediatric patients who receive a prescription for baricitinib in terms of total number of patients, demographics (age and sex) and select baseline diagnosis codes **(including RA, AD, and COVID-19).**	Missing information Use in paediatrics	Study progress reports Interim study report (corresponds to final study report date that was committed to at the time when RA was only approved indication) Final study report (corresponds to new final study report	Annually in the PSUR, submitted in April each year 31 March 2021 31 March 2023

			date committed to with addition of AD indication)	
I4V-MC-B025: Dermatologist Survey to Assess the Effectiveness of the Baricitinib Risk Minimisation Measures in Prescribers of Patients with Atopic Dermatitis (Planned)	Primary Objective: To assess the understanding of and adherence to the key risk minimisation messages and required mitigating actions in the HCP Educational Material and PAC among a sample of dermatologists, regarding: Use in pregnancy Infections Lipids VTE	Important Identified Risks Herpes zoster Important Potential Risks: Serious and opportunistic infections (including tuberculosis, *Candida* infections, PML) MACE as an outcome of hyperlipidaemia Foetal malformation following exposure in utero VTE	Final study report	30 September 2023

Abbreviations: AD = atopic dermatitis; ARTIS = Antirheumatic Therapies in Sweden; BSRBR = the British Society for Rheumatology Biologics Register; COVID-19 = coronavirus disease 2019; DILI = drug-induced liver injury; EU = European Union; GI = gastrointestinal; HCP = Healthcare Professional; MACE = major adverse cardiovascular events; PAC = Patient Alert Card; PBRER = periodic benefit-risk evaluation report; PML = progressive multifocal leukoencephalopathy; PSUR = periodic safety update report; PV = pharmacovigilance; Q = quarter; RA = rheumatoid arthritis; RABBIT = Rheumatoid Arthritis Observation of Biologic Therapy; US = United States; VTE = venous thromboembolic event.

PRAC assessment

The pharmacovigilance plan includes 6 ongoing/planned PASS for non-COVID 19 indications. For one of these PASS the MAH proposed to also include COVID 19 treated patients, namely the PASS (study I4V-MC-B016) Assessment of off-label use of baricitinib in the paediatric population in the United Kingdom.

Study I4V-MC-B016 - *the only one study in PV plan to be amended to include children with COVID-19 treated with baricitinib after submission of the application for extension of baricitinib indication to include treatment of coronavirus disease 2019 (COVID 19) in hospitalised adult and paediatric patients aged 10 years and older who require low-flow oxygen or non invasive ventilation/high flow oxygen.*

The interim results from 14V-MC-B016 are currently assessed under procedure No EMEA/H/C/004085/ MEA/009.2. This interim analysis identified a total of 6 paediatric patients

prescribed off-label baricitinib in the CPRD databases. These 6 patients comprised 0.63% of all patients (any age) in CPRD prescribed baricitinib; calculated 95% CI spanning 0.23% to 1.37%.

On this basis, it can be concluded that there are no experience and adequate data on the off-label use of baricitinib in children so far.

Suggestions for possible further additional pharmacovigilance activities will be possible after discussing all safety aspects as part of this procedure (EMEA/H/C/004085/II/0028).

Part V: Risk Minimisation Measures (including evaluation of the effectiveness of risk minimisation activities)

V.1 Routine Risk Minimisation Measures

Table 63 ***Description of Routine Risk Minimisation Measures by Safety Concern***

Safety concern	Routine Risk Minimisation Activities
Herpes zoster	[Routine risk communication:] SmPC Sections 4.4 and 4.8 PL Sections 2 and 4 [Routine risk minimisation activities recommending specific clinical measures to address the risk:] • SmPC Section 4.4 recommends that if an infection develops in patients with RA and AD, the patient should be monitored carefully, and Olumiant should be temporarily interrupted and not be resumed until the infection resolves. There is a further recommendation that, prior to starting treatment, all patients be brought up to date with all immunisations in line with current immunisation guidelines. • SmPC Section 4.4 also advises that if a patient develops herpes zoster, treatment should be temporarily interrupted until the episode resolves. • PL Section 2 advises that the patient should tell their doctor if they get painful skin rash with blisters during treatment as these can be signs of shingles.
Malignancies (including lymphoma and typically virus-induced malignancies, such as cervical and many oropharyngeal cancers)	[Routine risk communication:] SmPC Section 4.4 PL Section 2 [Routine risk minimisation activities recommending specific clinical measures to address the risk:] • PL Section 2 advises patients to tell their doctor or pharmacist before and during treatment if they have cancer because their doctor will have to decide if they can still be given Olumiant.
Serious and opportunistic infections (including tuberculosis, *Candida* infections, PML)	[Routine risk communication:] SmPC Sections 4.4 and 4.8 PL Section 2 [Routine risk minimisation activities recommending specific clinical measures to address the risk:] • SmPC Section 4.4 advises that the risks and benefits of treatment should be considered prior to initiating therapy in patients with active, chronic, or recurrent infections. **For treatment of RA and AD,** it also recommends that if an infection develops, the patient should be

Safety concern	Routine Risk Minimisation Activities
	monitored carefully and Olumiant should be temporarily interrupted for any infection that is not responding to standard therapy. Treatment should not be resumed until the infection resolves. • SmPC Section 4.4 advises that patients **with RA or AD** should be screened to rule out active TB and active viral hepatitis before starting Olumiant. • There is no reference to PML in the SmPC. • SmPC Section 4.4 advises that live, attenuated vaccines should not be used during or immediately prior to treatment. There is a further recommendation that, prior to starting treatment, all patients be brought up to date with all immunisations in line with current guidelines. • Section 2 of the PL advises patient that they need to talk to their doctor or pharmacist before and during treatment with Olumiant if they have an infection or if they often get infections. It also advises patents that they should tell their doctor if they get signs of TB, herpes zoster or have, or have previously had hepatitis B or C.
Myelosuppression (agranulocytosis)	[Routine risk communication:] SmPC Sections 4.2, 4.4, 4.8, and 5.3 PL Sections 2 and 4 [Routine risk minimisation activities recommending specific clinical measures to address the risk:] • SmPC Sections 4.2 and 4.4 recommend that treatment **for RA or AD** should not be initiated or should be temporarily interrupted in patients with an ANC < 1 x 109 cells/L, ALC < 0.5 x 109 cells/L, or haemoglobin < 8 g/dL. **For the treatment of COVID-19, the proposed SmPC advises that there is limited information on the use of baricitinib in patients with ANC < 1 x 10^9 cells/L, ALC < 0.2 x 10^9 cells/L or haemoglobin <8 g/d. It also recommends that the healthcare professional should consider if the potential benefits outweigh the potential risks of Olumiant treatment in these patients.** • PL Section 2 advises that patients **with RA and AD** may need blood tests prior to or during treatment to check if they have a low red blood cell count (anaemia) or low white blood cell count (neutropaenia or lymphopaenia) to ensure that treatment is not causing problems.
Myopathy including rhabdomyolysis	[Routine risk communication:] SmPC Section 4.8 (increases in CPK) PL Section 4 (increases in creatinine kinase) [Routine risk minimisation activities recommending specific clinical measures to address the risk:] None
Potential for drug-induced liver injury	[Routine risk communication:] SmPC Sections 4.2, 4.4, and 4.8 PIL Sections 2 and 4 [Routine risk minimisation activities recommending specific clinical measures to address the risk:] • SmPC Section 4.2 recommends that Olumiant is not recommended for use in patients with **RA and AD with** severe hepatic impairment. • Section 4.4 recommends that if increases in ALT or AST are observed during routine patient management and drug-induced liver injury is

Safety concern	Routine Risk Minimisation Activities
	suspected, Olumiant should be interrupted until this diagnosis is excluded. • Section 2 of the PL advises patients to speak to their doctor if they have, or have previously had, hepatitis B or C or if they have poor liver function.
MACE (as an outcome of hyperlipidaemia)	[Routine risk communication:] SmPC Sections 4.4 and 4.8 (hypercholesterolaemia and hypertriglyceridaemia) PL Sections 2 and 4 [Routine risk minimisation activities recommending specific clinical measures to address the risk:] • SmPC Section 4.4 recommends that **in patients with RA and AD,** lipid parameters should be assessed approximately 12 weeks following initiation of Olumiant therapy and thereafter patients should be managed according to clinical guidelines for hyperlipidaemia. • PL Section 2 advises patients may need blood tests before or while taking Olumiant to check if they have a high blood fat (cholesterol) to ensure that treatment with Olumiant is not causing problems.
Foetal malformation following exposure in utero	[Routine risk communication:] SmPC Sections 4.3, 4.6, and 5.3 PIL Section 2 [Routine risk minimisation activities recommending specific clinical measures to address the risk:] • SmPC Sections 4.3 and 4.6 state that pregnancy is a contraindication **in patients with RA and AD**. • SmPC Section 4.6 advises that patients **with RA and AD** of childbearing potential should use effective method of contraception to avoid becoming pregnant during treatment and for at least 1 week after the last treatment. **For patients with COVID-19, Section 4.6 advises that Olumiant should only be used during pregnancy if the potential benefit justifies the potential risk to the foetus.** • PL Section 2 • **RA and AD** o States that patients should not take Olumiant if they are pregnant or think that they may be pregnant. o Advises patients that if they are pregnant, think they may be pregnant, or are planning to have a baby, they should ask their doctor or pharmacist for advice before taking this medicine o States that patients should use an effective method of contraception to avoid becoming pregnant during treatment and for at least 1 week after the last Olumiant treatment o States that patients must tell their doctor if they become pregnant as Olumiant should not be used during pregnancy. • **COVID-19** o **States that Olumiant will be given only if the potential benefits of treatment outweigh the potential risks to the mother and the unborn child.**
VTE	[Routine risk communication:] SmPC Section 4.2, 4.4 and 4.8 PL Section 2

Safety concern	Routine Risk Minimisation Activities

	[Routine risk minimisation activities recommending specific clinical measures to address the risk:]
	• **SmPC Section 4.2 advises that, in patients with COVID-19, VTE prophylaxis is recommended unless contraindicated.**
	• SmPC Section 4.4 advises that
	  ○ Olumiant should be used with caution in patients with risk factors for DVT/PE such as older age, obesity, a medical history of DVT/PE, or patients undergoing surgery and immobilisation
	  ○ If clinical features of DVT/PE occur, treatment should be discontinued, and patients should be evaluated promptly followed by appropriate treatment.
	  ○ **In patients hospitalised with COVID-19, the use of prophylactic anticoagulation is recommended unless contraindicated.**
	• PL Section 2 advises patients to
	  ○ Talk to their doctor or pharmacist before and during treatment if they have previously had blood clots in the veins of their legs (DVT) or lungs (PE)
	  ○ Tell their doctor if they get a painful swollen leg, chest pain, or shortness of breath as these can be signs of blood clots in the veins.

Gastrointestinal perforation	[Routine risk communication:] None [Routine risk minimisation activities recommending specific clinical measures to address the risk:] None
Long-Term Safety	[Routine risk communication:] SmPC Sections 4.4 and 4.8 (hypercholesterolaemia and hypertriglyceridaemia) PL Sections 2 and 4 [Routine risk minimisation activities recommending specific clinical measures to address the risk:] No additional recommendations other than those already stated for malignancy and MACE
Use in Very Elderly (≥75 Years)	[Routine risk communication:] SmPC Sections 4.2, 4.4 (lymphocytosis), and 5.2 PL Section 3 [Routine risk minimisation activities recommending specific clinical measures to address the risk:] • SmPC Section 4.2 recommends that in patients ≥75 years **with RA or AD**, a starting dose of 2 mg is appropriate. **For patients with COVID-19 ≥75 years, no dose adjustment is required.**
Use in patients with evidence of hepatitis B or hepatitis C infection	[Routine risk communication:] SmPC Section 4.4 PL Section 2 [Routine risk minimisation activities recommending specific clinical measures to address the risk:] • SmPC Section 4.4 recommends that screening for viral hepatitis should be performed before starting treatment and that if HBV DNA is

Safety concern	Routine Risk Minimisation Activities
	detected, a liver specialist should be consulted to determine if treatment interruption is warranted. • Section 2 of the PL advises patients to speak to their doctor if they have, or have previously had, hepatitis B or C.
Use in patients with a history of or current lymphoproliferative disease	[Routine risk communication:] SmPC Section 4.4 PL Section 2 [Routine risk minimisation activities recommending specific clinical measures to address the risk:] • PL Section 2 advises patients to tell their doctor or pharmacist before and during treatment if they have cancer because their doctor will have to decide if they can still be given Olumiant.
Use in patients with active or recent primary or recurrent malignant disease	[Routine risk communication:] PL Section 2 [Routine risk minimisation activities recommending specific clinical measures to address the risk:] • PL Section 2 advises patients to tell their doctor or pharmacist before and during treatment if they have cancer because their doctor will have to decide if they can still be given Olumiant.
Use in Paediatric Patients	[Routine risk communication:] **SmPC Section 4.2 states that for patients with COVID-19 under the age of 10 years, the safety and efficacy have not been established.** PL Section 2 [Routine risk minimisation activities recommending specific clinical measures to address the risk:] • **PL Section 2 advises that Olumiant is not for use in children and adolescents younger than 18 years old with RA and AD. Olumiant is not for use in children under 10 years old with COVID-19.**

Abbreviations: AD = atopic dermatitis; ALC = absolute lymphocyte count; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; bDMARD = biologic disease-modifying antirheumatic drug; COVID-19 = coronavirus disease 2019; CPK = creatine phosphokinase; DNA = deoxyribonucleic acid; DVT = deep vein thrombosis; HBV = hepatitis B virus; JAK = Janus kinase; MACE = major adverse cardiovascular event; PE = pulmonary embolism; PL = Patient Information Leaflet; PML = progressive multifocal leukoencephalopathy; SmPC = Summary of Product Characteristics; TB = tuberculosis; VTE = venous thromboembolic event.

PRAC's assessment:

The proposed changes introduced by the MAH in the module V.1 in the RMP v. 11.1 are marked in bold text.

The wording change in SmPC and PL is being agreed in the relevant working documents, where corrections and comments are introduced in the form of change tracking. Thus, the scope of possible changes to module V.1. is carried out in parallel in other documents.

V.2 Additional Risk Minimisation Measures

Additional Risk Minimisation Activities applicable for RA and AD indications:

- Healthcare Professional (HCP) Educational Material
- Patient Alert Card (PAC)

Objectives:

The HCP educational material and PAC will inform prescribers and patients of the need to avoid using baricitinib during pregnancy. The materials will also provide advice on common signs and symptoms of infections and VTE, and the need to inform the doctor if these occur, as well as the need to monitor blood lipids during treatment.

Risks addressed:

- HZ
- Serious infections (including tuberculosis, *Candida* infections, PML)
- MACE (as an outcome of increased lipid parameters)
- Foetal malformation following exposure in utero
- Use in breastfeeding
- VTE

Rationale for the additional risk minimisation activity:

- Foetal malformation following exposure in utero: Nonclinical findings in 2 species (skeletal malformations) have not been refuted by limited pregnancy exposure in humans, and the significance remains unknown.

- Serious and opportunistic infections: Although infections overall affected about half of the study population exposed to baricitinib, the EAIR for serious infections in the All BARI RA population was 2.97 events per 100 PY. Since the number of patients treated in the CTs is relatively limited, the potential exists that more frequent and clinically significant outcomes of serious and opportunistic infections or different serious infections may be seen in everyday clinical practice.

- Hyperlipidaemia and hypercholesterolaemia are acknowledged ADRs of baricitinib treatment; however, the potential for adverse CV outcomes as a result of the observed lipid changes has been neither confirmed nor refuted due to limited long-term exposure

- VTE, specifically DVT and PE, are acknowledged ADRs of baricitinib treatment. Patients may not recognise a possible VTE and hence, it may be useful to inform them on the symptoms to watch out for and to recommend seeking medical advice immediately if they occur.

For all the safety concerns highlighted above, it is considered advisable to provide specific advice to patients who may not be aware of this eventuality, particularly in relation to use in pregnancy. Specific reference in the HCP communication is intended to ensure that they are aware of the key information to be provided to patients at the time of the initial prescription (i.e., to enable an informed discussion).

Target audience and planned distribution path:

The HCP educational material will be provided as agreed, at an individual Member State level, with the Competent Authorities.

PACs will be provided to the patient via 2 methods:

1. From the prescribing physician or HCP
2. In the pack as part of the patient leaflet with every prescription.

Plans to evaluate the effectiveness of the interventions and criteria for success:

a) A cross-sectional survey of HCPs will assess understanding of, and adherence to, the key risk minimisation messages on the PAC and HCP Educational materials (i.e., the required mitigating action for infections and VTE) and avoiding use in pregnancy and breastfeeding. HCPs will also be asked about periodic monitoring of patient lipid panels (Study I4V-MC-B025).

b) A cohort of patients who receive treatment with baricitinib will be observed for the occurrence of events related to the safety messages included in the risk minimisation activities (e.g., use of baricitinib during pregnancy, monitoring of blood lipids, use in patients with active TB, or hepatitis) (Study I4V-MC-B011). The pattern of use of baricitinib (e.g., among pregnant women and patients with active TB or hepatitis) will also be evaluated in this cohort.

Removal of additional risk minimisation activities

Not applicable.

PRAC's assessment

No changes made by MAH in module V.2. in comparison to the previous version of the RMP.

It seems that the main safety problems of baricitinib use in COVID-19 disease are infections, including opportunistic and severe infections, and thromboembolic events, as they can occur during the course of the disease itself and may be baricitinib-induced complications.

Suggestions for possible further additional risk minimisation measures and additional pharmacovigilance activities will be possible after discussing all safety aspects as part of this procedure (EMEA/H/C/004085/II/0028).

3.1. Overall conclusion on the RMP

Proposal of RMP v.11.3 was incomplete at the time it was submitted for this procedure. It contains data from Adaptive COVID-19 Treatment Trial 2 (ACTT2) and data from the KHAA/ COV-BARRIER study, but RECOVERY study data were not included in this version . These data should be completed in all relevant modules/sections of the RMP Part II modules S.III, S.IV and S.VII and maybe SVIII.

☒The changes to the RMP <and the changes to the conditions and obligations of MA> could be acceptable provided an updated RMP and satisfactory responses to the request for supplementary information in Annex 1 are submitted.

4. Changes to the Product Information

As a result of this variation, several sections of the SmPC are being updated. The Package Leaflet (PL) is updated accordingly.

The MAH should address the CHMP's comments on the product information (see Annex 6).

4.1.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The new indication targets a similar patient demographic as the representative test population that was used for the user testing performed for the initial marketing authorisation application. The proposed text modifications resulting from the new indication are minor and do not include text that is significantly different from that already user tested.

5. Benefit-Risk Balance

5.1. Therapeutic Context

5.1.1. Disease or condition

The MAH claimed the following therapeutic indication:

"Olumiant is indicated for the treatment of coronavirus disease 2019 (COVID 19) in hospitalised adult and paediatric patients aged 10 years and older who require low-flow oxygen or non-invasive ventilation/high flow oxygen (see section 5.1).".

COVID-19 is a respiratory disease caused by the novel coronavirus SARS-CoV-2. The virus has spread worldwide during 2020, causing WHO to declare a pandemic in March 2020. The virus infects the airways and causes a broad spectrum of respiratory symptoms ranging from asymptomatic infection to Severe Acute Respiratory Syndrome (SARS) and ARDS. The pandemic is still ongoing despite unprecedented efforts to control the outbreak.

5.1.2. Available therapies and unmet medical need

The management of COVID-19 cases has developed during 2020 and includes supportive care, which may include fluid therapy, oxygen support, and supporting other affected vital organs.

The major classes of therapies developed to treat COVID-19 infection in hospitalised patients are antiviral therapies, immunosuppressive/anti-inflammatory therapies, and monoclonal antibodies. Veklury® (remdesivir), an antiviral therapy, is approved in Europe for the treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment (VEKLURY SmPC 2021). In addition, dexamethasone, an anti-inflammatory therapy, is approved in Europe for the treatment of COVID-19 in adult and adolescent patients aged 12 years and older with a body weight of at least 40 kg who require supplemental oxygen therapy (Dexamethasone SmPC). Several monoclonal antibodies have now been approved for treatment of confirmed COVID-19 in patients who do not require supplemental oxygen and who are at high risk of their COVID-19 disease becoming severe or for prevention of COVID-19 (including Ronapreve, Regkirona, Xevudy and Evusheld). Kineret has been approved for adult patients with pneumonia requiring supplemental oxygen (low or high flow) who are at risk of progressing to severe respiratory failure as defined by plasma suPAR level of ≥6 ng/mL and

RoActemra is indicated for treatment of adult patients with coronavirus disease who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation.

In Europe and other countries, an important unmet need remains for patients hospitalised with more severe disease.

5.1.3. Main clinical studies

Initially the data of two pivotal studies were provided to support the current extension of the indication (EoI) to include treatment of patients with COVID-19, the ACTT-2 study and the KHAA/COV-BARRIER study. Both the ACTT-2 and KHAA were multicentre, randomized, blinded, placebo-controlled Phase 3 trials. ACTT-2 evaluated the efficacy and safety of baricitinib (n=515) and placebo (n=518) on a background regimen of remdesivir. KHAA evaluated the efficacy and safety of baricitinib (n=764) and placebo (n=761) on a background regimen of local SOC.

During the second round of this procedure, topline results in patients with baseline OS 7 included in the KHAA trial per addendum 5 (n=51 patients treated with baricitinib and n=50 patients treated with placebo) and topline results of the ACTT-4 were provided. The ACTT-4 is a randomized phase 3 superiority trial, comparing baricitinib + remdesivir (n=516) with dexamethasone + remdesivir (n=494) in the treatment of patients hospitalized with COVID-19. Enrolment was closed prematurely, as the study met predefined futility criteria indicating that neither treatment regimen studied was likely significantly better than the other.

During the third round of this procedure, topline results of the baricitinib arm of the RECOVERY trial were provided. The RECOVERY trial is a randomised, controlled, open-label platform trial, assessing multiple possible treatments in patients hospitalised for COVID-19. In the baricitinib arm of the trial, 8156 patients were randomised to receive baricitinib + SoC or SoC alone.

5.2. Favourable effects

In the ACTT-2 trial, statistical significance was met for **time to recovery** (primary endpoint), which was shortened by one day in patients treated with baricitinib. The median time to recovery was 7 days (95% CI: 6.0, 8.0) compared to 8 days (95% CI: 7.0, 9.0) in the baricitinib + remdesivir and placebo + remdesivir groups respectively (rate ratio (RR) for recovery 1.16; 95% CI 1.01- 1.33; p=0.03). In KHAA, time to recovery was also shortened by one day in patients treated with baricitinib. The median time to recovery was 10 days in the baricitinib + SOC group and 11 days in the placebo + SOC group (RR 1.11; 95% CI 0.99 - 1.24]).

A statistically significant smaller proportion of patients treated with baricitinib + remdesivir compared to patients treated with placebo + remdesivir **died or progressed to ventilation** (23% vs 29%; OR 0.73; p = 0.03) in the ACTT-2 trial. The KHAA trial also showed a numerical trend towards less disease progression in the baricitinib group. The proportion of patients who progressed to ventilation or death was 30.5% (27.2, 33.8) for placebo-treated patients and 27.8% (24.6, 31.0) for baricitinib treated patients (OR for disease progression 0.85; 95%CI 0.67- 1.08; p=0.18).

For **all-cause mortality** by Day 29: a numerical reduction in mortality was observed in the baricitinib group, with mortality rates of 4.5% for baricitinib + remdesivir versus 7.3% for placebo + remdesivir (HR = 0.63 [95% CI: 0.37, 1.05]; p=.075) in the ACTT-2 trial. Also in KHAA, a reduction in Day 28 all-cause mortality was observed with mortality rates of 8.1% for baricitinib versus 13.1% for placebo treated patients (38.2% relative reduction; HR = 0.57; 95% CI 0.41 - 0.78). Of note, topline results of the Day 60 mortality analysis of the KHAA trial were consistent with the Day 28 results and remained statistically significantly lower for baricitinib + SOC (10.3%) vs placebo + SOC (15.2%).

In ACTT-4, the primary endpoint of the study (superiority of 1 group versus another) was not met since a similar proportion of patients either died or required mechanical ventilation by Day 29 in the baricitinib + remdesivir group compared with the dexamethasone + remdesivir group (5.2% of patients in the baricitinib + remdesivir group had died as compared 6.1% in the dexamethasone + remdesivir group). Time to recovery and the odds of clinical improvement on the NIAID OS by Day 15 were both similar between the treatment groups.

In the RECOVERY trial 4148 patients were randomly allocated to receive baricitinib +SoC and 4008 patients were randomly allocated to receive SoC, of whom 513 patients in the baricitinib group (12.3%) and 546 (13.6%) patients in the SoC group had died by Day 28 (primary analysis ITT population). A reduction in 28-day mortality of 1.2% was observed in patients treated with baricitinib. As observed from the secondary outcome measures in this trial, patients treated with baricitinib had a nominal significantly higher chance to be discharged alive within 28 days compared with usual care (80% vs. 78%; age-adjusted rate ratio 1·10, 95% CI 1·04 to 1·15; median 8 days [IQR 5 to 17] vs. 8 days [IQR 5 to 20]) and a lower risk of progressing to the composite secondary outcome of invasive mechanical ventilation or death (16% vs. 17%, age-adjusted risk ratio 0·90, 95% CI 0·81 to 0·99) (secondary outcome measures in the RECOVERY trial).

5.3. Uncertainties and limitations about favourable effects

Initially, the proposed indication statement, included treatment of paediatric patients aged 10 years and older. As no clinical and pharmacokinetic data were provided for the paediatric population, inclusion of the paediatric population in the indication statement was considered not acceptable by the CHMP and a major objection (MO) was raised. In their response, the MAH submitted a revised product information with an indication limited to the proposed indication has been limited to the adult population.

The KHAA study did not meet its primary endpoint, and as a consequence, no secondary endpoints met multiplicity-controlled statistical significance.

In ACTT-2, the clinical relevance of a one-day improvement in time to recovery -which was only marginally statistically significant- is questionable. Further, the clinical relevance of time to recovery may be debated as initial recovery may be followed by a subsequent relapse of COVID disease. A sensitivity analysis censoring patients readmitted after initial recovery has been provided. Time to recovery after censoring readmittance still shows a benefit for the baricitinib + remdesivir group over the placebo + remdesivir group that is consistent with the analysis of the primary endpoint as (median time to recovery in this sensitivity analysis: baricitinib + remdesivir = 7.0 days, placebo + remdesivir = 8.0 days, hazard ratio (HR) 1.13, 95% CI 0.98 to 1.29 (statistical significance not reached)). The proportion of recovered patients that reached a sustained recovery status was marginally larger in the placebo group (88.2% vs.87.3%).

In ACTT-2, a substantial part of the study population did not recover and did not die by Day 29. No data are available after Day 29, and thus uncertainty remains regarding the large proportion of patients for whom clinical status is not known.

External validity of the ACTT-2 results is questionable as all patients in this study received remdesivir and only 20% received corticosteroids, while currently corticosteroids are part of standard of care for the population envisioned in the indication statement.

The effect on mortality as an important secondary endpoint in ACTT-2 was not statistically significant, and in KHAA, the effect on mortality failed to demonstrate multiplicity-adjusted statistical significance.

Although a trend towards comparable efficacy of baricitinib + remdesivir vs dexamethasone + remdesivir in OS 5 and OS 6 hospitalised patients could be observed in ACTT-4, this trial was designed to demonstrate superiority and was prematurely halted for futility when no significant benefit for one of both therapies could be observed. Based upon the SAP of the ACTT-4 trial and the accompanying futility analysis plan, neither the possibility for testing for equivalence (or non-inferiority) nor an equivalence (or non-inferiority) margin has been pre-defined.

The reduction in all-cause mortality in baricitinib treated patients observed as the primary outcome measure of the RECOVERY trial, only reached statistical significance after adjusting for baseline covariates. Given the lack of clearly pre-specified conditions for an adjusted analysis and the discrepancy between the variable on which "imbalance" (0.8 year difference in mean age with overlapping standard deviations) is observed (continuous age) and the variable on which the corrected estimate is based (age categories), the age-adjusted RR is not acceptable as a primary efficacy measure. Thus the unadjusted analysis is considered the main analysis and its outcome does not reach statistical significance. The uncertainty surrounding the conclusion of efficacy of baricitinib is further perplexed by the significance level to be employed in the main analysis. In addition to the concerns raised with respect to the adjusted analysis, it should be noted that the significance level of 0.01, implied by the decision to stop recruitment, is not reached, even with the age-adjusted analysis.

Apparently, not all patients received their allocated treatment to baricitinib (only 90%) and in the 10% not receiving treatment, mortality was high (>20%). Reasons for not receiving baricitinib and high mortality in this group remain unclear. Furthermore, it became clear that new RECOVERY data are now available and ideally the updated analysis should be provided for review. For the secondary RECOVERY endpoints, only age adjusted rate ratios have been provided and the results should thus be interpreted with caution.

5.4. Unfavourable effects

The safety analysis primarily considers the pooled data of the 28/29 days of follow-up of studies ACTT-2 and KHAA in patients having received at least one study administration after randomisation.

Overall, for the treatment of COVID-19, there were no new or significant findings, and the safety profile is consistent with the established safety profile of baricitinib (for RA and AD). However, some ADRs (AST ≥3 × ULN, ALT ≥3 × ULN, PE, DVT, and neutropenia less than 1000 cells/mm^3) were reported more frequently for the COVID-19 population compared to the RA, AD and AA populations.

Treatment-emergent **AEs** were reported by 43% of patients in the pooled baricitinib group compared to 46% of patients in the pooled placebo group. At the PT level, there was a tendency that AEs describing manifestations and complications of Covid-19 (respiratory failure, acute respiratory failure, pneumonia, septic shock, glomerular filtration rate decreased/acute kidney injury) occurred more frequently in the placebo group as compared to the baricitinib group.

SAEs were reported for 16% of patients in the pooled baricitinib group and 19% in the pooled placebo group. The most-reported SAEs in the baricitinib group as compared to placebo were: Respiratory failure (3.1% *versus* 4.3%); Acute respiratory failure (2.8% *versus* 3.6%); Septic shock (1.4% *versus* 3.6%).

The occurrence of **death** was lower in the baricitinib group as compared to placebo (see Efficacy section). With few exceptions, the cause of death was due to Covid-19 in both treatment groups of both studies. In study KHAA, with a 60-day follow-up, the ~5% percentage points of difference in survival over the 28-day period, in favour of baricitinib, was maintained up to 60 days.

Treatment-emergent **infections** were reported by 12.6% patients in the pooled baricitinib group compared with 14.5% patients in the pooled placebo group. The most frequently reported treatment-emergent infection reported for baricitinib was Pneumonia (sic), with 2.6% *versus* 3.3% on placebo. It was inferred that the occurrence of new (non-SARS-Cov2) infections was lower in the baricitinib group as compared to the placebo group (11% versus 12%). Opportunistic infections occurred in 1.0% of the baricitinib group as compared to 0.9% in the placebo group. The numbers of treatment-emergent (non-Covid-19) serious infectious events were 56 events in the integrated baricitinib group compared with 78 events in the integrated placebo group.

Treatment-emergent **venous thromboembolic events** were reported by 3.3% of patients treated with baricitinib and by 2.8% of patients treated with placebo. Pulmonary embolism and deep vein thrombosis were reported by 1.4% and 1.5% in the pooled baricitinib group and 0.9% and 1.3% in the pooled placebo group. Pulmonary embolism and Deep vein thrombosis were SAE in 1.4% and 0.4% of patients in the baricitinib group compared to 0.6% and 0.5% of patients in the placebo group. In both Study ACTT-2 and Study KHAA, VTE prophylaxis was recommended, and this was used for the vast majority (97.5%) of patients. The MAH included in Section 4.2 of the SmPC a recommendation for Venous Thromboembolism (VTE) prophylaxis unless contraindicated which is acceptable.

Safety data were stratified for **concomitant use of corticosteroids**. In ACTT-2, treatment-emergent adverse events were reported in 60% of the patients in the baricitinib + remdesivir + steroid group compared with 59% of the patients in the placebo + remdesivir + steroid group. In study KHAA, treatment-emergent adverse events were reported by 43% of patients in the baricitinib + SOC group versus 46% of patients in the placebo + SOC group when baseline steroid was prescribed. The MAH included in Section 4.2 of the SmPC a statement that "Baricitinib may be used with or without corticosteroids and with or without remdesivir" which is acceptable.

In ACTT-2, for patients **older than 65 years** of age, SAEs were less frequently reported in the baricitinib group compared to the placebo group. Only in patients between 65-74, infections were more frequent on baricitinib as compared to placebo (12% *versus* 9.6%). In KHAA, Serious adverse events and deaths were less frequently reported in the baricitinib group compared with placebo.

5.5. Uncertainties and limitations about unfavourable effects

Different collection of AEs

In study ACTT-2 only severe and life-threatening events (grade 3 and 4) were collected, while in KHAA also mild and moderate (grade 1 and 2) AEs were collected. Given the life-threatening nature of Covid-19 for patients hospitalised and in need of oxygen, and given the many manifestations, sequelae and complications of Covid-19, restriction to grade 3 and 4 AEs can be understood. The uncertainty following the different collection of AEs (grade 3 and 4 in ACTT-2 versus all grades in KHAA) can be mitigated by paying attention to the study-specific results, in addition to the pooled results.

New infections

From the pooled data of studies ACTT-2 and KHAA it seems that new (non-SARS-Cov2) infections are lower in the baricitinib group than the placebo group (11% versus 12%). However, during data collection and presentation no clear difference was made between infection AEs that are probable manifestations, sequels or complications of Covid-19, and new (thus non-SARS-Cov-2/Covid-19) infections and serious infections. However, the difference between baricitinib and placebo is considered small, and overall there is no indication that baricitinib would lead to more new (non-Covid-19) infectious events.

Special populations

According to the SmPC text proposed by the MAH, patients hospitalized because of Covid-19 and: severe hepatic failure, pre-existing (or new) serious infections, eGFR between 15 and 30 mL/min, ALC< 0.2 x 10^9 cells/L, ANC< 1 x 10^9 cells/L , or haemoglobin < 8 g/dL could be treated with baricitinib. Given the seriousness of the underlying condition and given that all patients are standardly monitored, while treatment is for a relatively short period of time, this was considered acceptable. This is in deviation of the warnings and recommendations for the treatment of Rheumatoid arthritis, alopecia areata and Atopic dermatitis.

The clinical experience is very limited for use in very elderly (≥ 75 years) (missing information in the RMP). Since patients with COVID-19 are being monitored in a hospital environment and will be treated for a short period of time, it is acceptable to keep the same dose for some special populations (patients aged 75 years or older, and also patients with a history of chronic or recurrent infections or with mild or moderate hepatic impairment). The following statement is included in the Section 4.2 of the SmPC which is acceptable: "COVID-19: No dose adjustment is required in patients ≥ 75 years. The clinical experience in patients ≥ 75 years is limited."

5.6. Effects Table

Table 64 ***Effects Table for Baricitinib EoI to include treatment of COVID-19***

Effect		Short description	Unit	Baricitinib	Placebo	Uncertainties / Strength of evidence	Ref.
Favourable Effects ACTT-2 (background regimen of RDV, 20% concomitant corticosteroids)							
Primary	Recovery	Median time to recovery by Day 29	Median Days (95%CI)	7.0 (6.0, 8.0)	8.0 (7.0, 9.0)	RR 1.15, (95%CI 1.00, 1.32), p=.043	**ACTT-2 CSR**
Secondary	Disease progression	Proportion of patients progressing to ventilation or death through Day 29	% (95%CI)	23 (19, 27)	29 (25, 33)	OR 0.73, (95%CI 0.55, 0.97), p=.030	
Secondary	Mortality	All cause mortality Day 1-Day 29	n (%)	23 (4.5)	37 (7.3)	HR 0.63, (95%CI 0.37, 1.05), p=.075	
Favourable Effects KHAA (background regimen of SOC, 80% concomitant corticosteroids)							
Primary	Disease progression	Proportion of patients progressing to ventilation or death through Day 28	% (95%CI)	27.8 (24.6, 31.0)	30.5 (27.2, 33.8)	OR 0.85, (95%CI 0.67, 1.08), p=.180	**KHAA CSR**
Secondary	Recovery	Median time to recovery by Day 28	Median Days (95%CI)	10.0 (9.0, 11.0)	11.0 (10.0,12.0)	RR 1.11, (95%CI 0.99, 1.24), p=.145	
Secondary	Mortality	All-cause mortality Day 1-Day 28	n (%)	62 (8.1)	100 (13.1)	0.57, (0.41, 0.78), nominal p=.002, *(no multipl. correction)*	
Favourable Effects RECOVERY (background regimen of SOC, 95% concomitant corticosteroids)							
Primary	Mortality	All-cause mortality Day 1-Day 28	n (%)	12.4	13.6	Age unadjusted RR 0.90, p=0.09, (95% CI 0.80-1.02); Age adjusted RR 0.87, p=0.026 (95% CI 0.77-0.98)	**RECOVERY** publication and supplementary material*
Unfavourable effects							

Effect	Short description	Unit	Baricitinib	Placebo	Uncertainties / Strength of evidence	Ref.
N			1257	1261		**ACTT-2 and KHAA**
AE overall	Proportion with ⩾ 1 TEAE	n (%)	544 (43%)	576 (46%)		
SAE overall	Proportion with ⩾ 1 TESAE	n (%)	197 (16%)	244 (19%)		
Infections overall	Proportion with ⩾ 1 Infection	n (%)	159 (13%)	183 (15%)		
Serious		n (%)	76 (6.0%)	94 (7.5%)		
New		n (%)	137 (10.7%)	149 (12.1%)	To be confirmed	
Opportunistic		n (%)	12 (1.0%)	11 (0.9%)		
Venous Thrombotic Events	Proportion with VTE	n (%)	41 (3.3%)	35 (2.8%)		
Pulmonary embolism		n (%)	18 (1.4%)	11 (0.9%)		
Deep Venous Thrombosis		n (%)	19 (1.5%)	16 (1.3%)		

Abbr. OS= NIAID ordinal scale; RDV= remdesivir; SOC= standard of care; Notes: No multiplicity correction performed for sec outcome measures KHAA

**RECOVERY publication and supplementary material accessed via:*

https://www.medrxiv.org/content/10.1101/2022.03.02.22271623v1.full-text and

https://www.medrxiv.org/content/10.1101/2022.03.02.22271623v1.supplementary-material

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

In ACTT-2 an effect of baricitinib on disease progression was observed, demonstrated by one-day improvement in time to recovery. A clinical relevance of this one day faster recovery can be debated. In a sensitivity analysis censoring patients readmitted after initial recovery, the observed benefit in time to recovery was no longer statistically significant. In the KHAA study, baricitinib could not demonstrate an effect on disease progression defined as the proportion of patients progressing to ventilation or death by Day 28. However, for the clinically relevant endpoints of time to recovery, all-cause mortality and odds of clinical improvement by Day 14, numerical improvements were observed in the different outcome measures. These were consistent with the effect size seen in the ACTT-2 trial for these endpoints. Overall, both ACTT-2 and KHAA suggest a potential but inconclusive beneficial effect of baricitinib on disease progression in patients with COVID-19 who need supplemental oxygen.

Regarding the important secondary favourable effect of all-cause mortality, baricitinib showed a 38% relative reduction in both trials. This reduction in overall mortality was consistent for patients with baseline ordinal scales 5 and 6, which is also the currently proposed target population. However, although the relevance of mortality as an outcome is not debated, the questionable effects on the primary endpoints in the pivotal trials cannot be disregarded.

While the observed reduction in mortality in patients with baseline OS 7 (included per addendum 5 of the KHAA study) supports the potential benefit in mortality observed in other baseline OS subgroups in this study, these data do not alleviate CHMP's concern regarding the overall strength of evidence obtained from KHAA. Moreover, mortality in baseline OS 7 in study ACTT-2, was not significantly different between treatment arms and results for this subgroup thus remain inconclusive.

Although the topline results of ACTT-4 (comparing baricitinib with corticosteroids on a background regimen of remdesivir) may be acknowledged, this trial was designed to demonstrate superiority and was unfortunately prematurely halted for futility when no significant benefit for one of both therapies could be demonstrated. Neither the possibility for testing for equivalence (or non-inferiority) nor an equivalence (or non-inferiority) margin has been pre-defined. Therefore, any inferential analysis and interpretation is not considered to be appropriate. One of the requirements for switching a superiority trial objective is that the acceptable non-inferiority margin was pre-defined or can be justified (the latter is likely to prove difficult and to be limited to rare cases where there is a widely accepted value for Δ.) – (CPMP/EWP/482/99, POINTS TO CONSIDER ON SWITCHING BETWEEN SUPERIORITY AND NON-INFERIORITY). Thus, this trial does not provide the confirmatory evidence needed to ensure baricitinib has a beneficial effect for patients with COVID-19 in need of oxygen.

Although the RECOVERY data point towards a reduction in all-cause mortality in baricitinib treated patients, this finding only reached statistical significance after adjusting for baseline covariates. Given the lack of clearly pre-specified criteria to apply an adjusted analysis, the post-hoc age-adjusted RR is not considered being acceptable as a primary efficacy measure. In addition an updated datacut is available and updated analyses should be provided for review.

The safety profile of baricitinib was overall positive. From the pooled and individual data of studies ACTT-2 and KHAA, there appeared to be no new safety signals for baricitinib. There only were two common (>2%) AEs that occurred numerically more often with baricitinib as compared to placebo: glomerular filtration rate decreased and constipation. Both are not proposed as (potential) risks of baricitinib. It is relevant that in baricitinib treated patients, serious and opportunistic infections did not occur more

frequently. From both trials, ACTT-2 and KHAA, it does not appear that concomitant use of corticosteroids leads do a different safety profile of baricitinib, as compared to placebo. Therefore, from a safety perspective, baricitinib can be used with concomitant corticosteroids.

Infections, including serious and opportunistic infections, are an identified risk for baricitinib. It appears that infections and serious infections occurred less frequently with baricitinib as compared to placebo, and opportunistic infections were not more frequent with baricitinib. It seems that the occurrence of new (non-SARS-Cov2) infections also is lower in the baricitinib group as compared to the placebo group. It is relevant that treatment with baricitinib would not systematically lead to secondary infections in hospitalised patients.

Pulmonary embolism (PE) and deep venous thrombosis (DVT) are ADRs of baricitinib treatment, and the occurrence of venous thrombotic events (VTE) is an important potential risk for baricitinib. In the trials, treatment-emergent VTEs were more frequent in patients treated with baricitinib than with placebo. The occurrence of VTE was higher than in the RA and AD trials. This is likely caused by Covid-19 itself, but it may also be caused by corticosteroids. VTE prophylaxis was used in nearly all patients of both studies and is recommended in the SmPC. Given the existing risk factors for VTE, there is no clear route for further risk minimisation.

5.7.2. Balance of benefits and risks

The overall BR balance of baricitinib in the claimed indication is undetermined from a benefit perspective.

The ACTT-2 study demonstrated that the combination of baricitinib plus remdesivir had a beneficial effect on time to recovery, progression to ventilation or death, as compared to remdesivir alone. However, the one-day improvement of time to recovery that was only marginally statistically significant is of unknown clinical relevance. External validity of the study results is questionable as all patients in this study received remdesivir and only 20% received corticosteroids, while currently corticosteroids are part of standard of care for the population envisioned in the indication statement. In addition, the numerical reduction in mortality that was observed in the baricitinib group was not statistically significantly different from placebo.

The KHAA study provided additional data without background remdesivir treatment and with the allowance of background steroids, which is the standard of care in current treatment guidelines. However, this study failed to meet its primary endpoint of reducing the risk of ventilation or death progression; therefore, inference concerning mortality could not reach multiplicity-controlled statistical significance.

Although consistency was observed in the favourable effects of baricitinib across both trials, effect sizes were limited and statistical significance was not met for key endpoints in both studies.

A head to head comparison of baricitinib + remdesivir vs. dexamethasone + remdesivir for the treatment of patients with COVID-19 has been performed in the ACTT-4 trial, with the aim to show superiority of either of the 2 regimens. However, enrolment in this superiority trial has been closed prematurely based upon predefined futility criteria, and post-hoc conclusions on non-inferiority cannot be drawn, although a trend may be observed towards comparable efficacy of baricitinib and dexamethasone. Thus, this trial cannot provide confirmatory evidence needed to ensure baricitinib has a beneficial effect for patients with COVID-19 in need of oxygen.

In line with the ACTT-2 and COV-BARRIER results, the baricitinib RECOVERY data illustrate a small effect in favour of baricitinib across different clinically relevant outcome measures, including all-cause mortality at Day 28. However, focusing on the unadjusted analysis of Day 28 all-cause mortality as the primary

analysis for this trial, the primary outcome of the study was not met. Moreover, an updated datacut is available and updated analyses should be provided for review.

The safety profile of baricitinib is overall acceptable. The occurrence of AEs, SAEs, discontinuations due to an AE, infections, was overall lower for baricitinib as compared to placebo, in both trials. The safety data are overall consistent with the known safety profile of baricitinib for the approved indications, including infections and VTE. No new safety signals were identified.

5.7.3. Additional considerations on the benefit-risk balance

NA

5.8. Conclusions

In conclusion, the application for EoI to include COVID-19 patients in need of supplemental oxygen has been based on one trial that met its primary endpoint (ACTT-2) and two trials that -according to regulatory standards- failed to meet their primary endpoints (KHAA and RECOVERY). Although the relevance of mortality as an outcome is not debated, the limited clinical relevance of the primary endpoint in ACTT-2 and the lack of statistical significance of the primary endpoints for KHAA and RECOVERY, cannot be disregarded. The overall benefit / risk of baricitinib in the claimed indication is currently negative.